Functional cerebral asymmetries of emotional processes in the healthy and bipolar brain

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Functional cerebral asymmetries of emotional processes in the healthy and bipolar brain

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Declaration

I confirm that no part of the material offered has previously been submitted by me for a degree in this or in any other University. If material has been generated through joint work, my independent contribution has been clearly indicated. In all other cases material from the work of others has been acknowledged and quotations and paraphrases suitably indicated.

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Summary

The perception and processing of emotions are of primary importance for social interaction, which confers faculties such as inferring what another person's feels. Brain organisation of emotion perception has shown to primarily involve right hemisphere functioning. However, the brain may be functionally organised according to fundamental aspects of emotion such as valence, rather than involving processing of emotions in general. It should be noted, however, that emotion perception is not merely a perceptual process consisting in the input of emotional information, but also involves one's emotional response. Therefore, the functional brain organisation of emotional processing may also be influenced by emotional experience. An experimental model for testing functional cerebral asymmetries (FCAs) of valenced emotional experience is uniquely found in bipolar disorder (BD) involving impaired ability to regulate emotions and eventually leading to depressive or manic episodes. Previous models have only explained hemispheric asymmetries for manic and depressive mood episodes, but not for BD euthymia.

The present thesis sought to investigate FCAs in emotional processing in two major ways. First, FCAs underlying facial emotion perception under normal functioning was examined in healthy controls. Secondly, functional brain organisation in emotional processing was further investigated by assessing FCAs in the bipolarity continuum, used as an experimental model for studying the processing of emotions. In contrast with previous asymmetry models, results suggested a right hemisphere involvement in emotional experience regardless of valence. Atypical FCAs were found in euthymic BD patients reflecting inherent aspects of BD functional brain organisation that are free of symptomatic influence. Also, BD patients exhibited atypical connectivity in a default amygdala network particularly affecting the right hemisphere, suggesting intrinsic mechanisms associated with internal emotional states. Last, BD patients were associated with a reduced right hemisphere specialisation in visuospatial attention, therefore suggesting that right hemisphere dysfunction can also affect non-emotional processes. Taken together, the findings emphasize a BD continuum model relying on euthymia as a bridging state between usual mood and acute mood phases.

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Chapter 1

Introduction

From a psychological perspective, the term *emotion* is defined as an individual's reactions to appropriately evocative stimuli that include appraisal, expression, experience, arousal, and/or goal-directed activity (Plutchick, 1984). Emotional expressions are typically arranged into six universally recognised basic categories (fear, happiness, sadness, disgust, anger, and surprise; Ekman & Friesen, 1976; Izard, 1971) that are similar across different backgrounds and cultures (Ekman & Friesen, 1976; Izard, 1971, 1994). Perception of emotions involves processing of simple features of the stimulus, or differentiating one stimulus from another. The recognition of emotions can be seen as a distinct process connecting this perception to stored knowledge. Whereas perception and recognition of emotions consist on the ability to discern one's own and other's emotions based on "situational and expressive cues that have some degree of cultural consensus as to their emotional meaning" (Saarni, 1999, p. 106), the experience of emotion is what it feels like from a first-person perspective as an emotion unfolds (Barrett, Gendron, & Huang, 2009).

Emotional processing is a fundamental function of the brain that allows perceiving or consciously feeling an emotion and subjectively describing what the emotion feels like (Barrett et al., 2009). The neural correlate of emotional processing involves a number of brain regions including occipital temporal cortices, amygdala, orbitofrontal cortices, and right fronto-parietal cortices (Adolphs, 2002a; see Fig. 1).

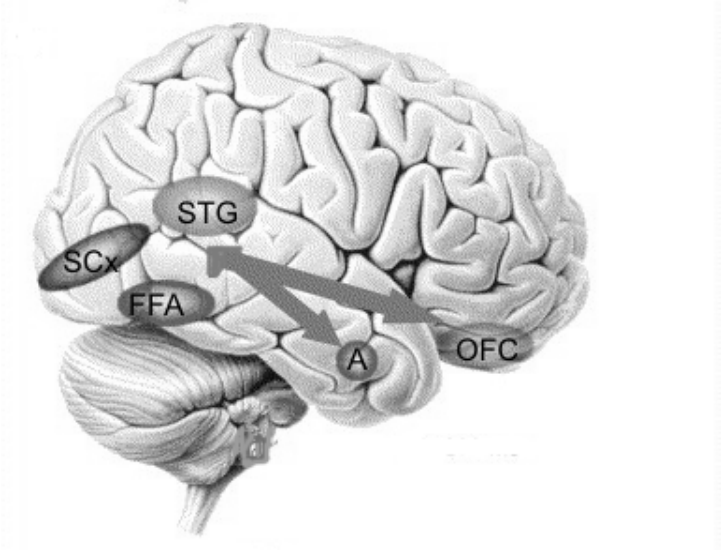

Figure 1. An interconnected brain network underlying the perception of emotion involves functionally and anatomically connections between the amygdala (A), prefrontal areas including the orbitofrontal cortex (OFC), and right posterior areas including the superior temporal gyrus (STG), fusiform gyrus (FFA), and striatal cortex (SCx). Adapted from Adolphs (2002).

The role of the amygdala for emotional processing has been suggested by findings of amygdala activation for emotion perception (Belin, Fecteau, & Bedard, 2004; Fecteau, Belin, Joanette, & Armony, 2007; Gur et al., 2002; Habel et al., 2007; Phillips et al., 1998; Sabatinelli et al., 2011; Sander & Scheich, 2001) and cases of bilateral amygdala lesions exhibiting impoverished response to fear-provoking situations (Jacobson, 1986; Broks et al., 1998; Calder, Lawrence, & Young, 2001). Also, an involvement of the orbitofrontal cortex, especially on the right, has been shown by lesion studies reporting impaired recognition of emotions from the face and voice which correlated with alterations in emotional experience (Hornak, Rolls, & Wade, 1996). Emotion processing has also been associated with the involvement of right fronto-parietal cortices, supported by the finding that lesions in somatosensory cortices in the right hemisphere compromise recognition of facial emotion (Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000).

In line with the close overlap between neural structures associated to perception and experience of emotion, it has been shown that inducing mood states enhances sensitivity to emotion-congruent information. For example, inducing happy, sad and neutral states, showed more accurate identification of emotion-congruent expressions

from computer animated images than those that were incongruent with the experienced mood (Niedenthal et al., 2000).

1.1. Perception and experience of emotion

The ability to perceive and recognise emotional expressions is of primary importance for humans to socially interact with each other (Nachson, 1995). For example, one can quickly infer the state of mind of one's peers and adjust one's behaviour accordingly from the perception of facial or emotional prosodic expressions. Likewise, being able to undergo emotional experiences is a prerequisite for empathy (Davis, 1994). In this regard, feeling an emotion has implications for satisfactory social functioning because it facilitates understanding of other's thoughts and emotions, nonverbal communication, and adaptive, prosocial responding to others (Spreng, Mar, & Kim, 2009; Zahn-Waxler, Robinson, & Emde, 1992).

Given that perception and experience of emotion are tightly interconnected, one would expect that the perception of emotion in another person and experiencing that emotion oneself involve overlapping neural substrates. In fact, previous findings have suggested that specific brain structures are critical areas for the perception and experience of specific emotions. Specifically, the amygdala has been implicated in fear (Calder et al., 2001; Davis, 1992; Feinstein, Adolphs, Damasio, & Tranel, 2011; Phan, Wager, Taylor, & Liberzon, 2002; Sprengelmeyer et al., 1999), the insular cortex has been implicated in disgust (Adolphs et al., 2003; Calder, Keane, Manes, Antoun, & Young, 2000; Calder, Lawrence, & Young, 2001; Jabbi, Bastiaansen, & Keysers, 2008; Stark et al., 2003; Wicker et al., 2003), the subgenual ACC has been implicated in sadness (Drevets et al., 1997; Mayberg et al., 1999; Phan et al., 2002, Smith et al., 2011), and the orbitofrontal cortex has been implicated in anger (Vytal & Hamann, 2010). The majority of this research comes from lesion studies based on the assumption that damage to these regions should diminish, or even abolish, one's ability to perceive and or experience the specific emotion. Following this prediction, a patient with bilateral amygdala lesions has shown impaired recognition of fear from facial and prosodic cues. He also revealed an abnormal score on a self-assessment questionnaire tapping the experience of fear but normal scores for similar questionnaires assessing his experience of anger and disgust (Sprengelmeyer et al., 1999). Moreover, it has been shown that electrical stimulation of the amygdala in

human subjects undergoing surgery for epilepsy can induce various reactions, but when an emotion is reported it is invariably fear (Halgren, 1992). Similarly, a patient with insula and putamen damage exhibited deficits in recognising disgust from facial expression and emotional prosody and was less disgusted than controls by disgust-provoking scenarios (Calder et al., 2000). These deficits are consistent with findings of impaired facial recognition of disgust in people with Huntington's disease (Sprengelmeyer et al., 1996), usually involving insula damage (Weeks et al., 1997). Last, sadness and anger have been suggested to rely on the subgenual anterior cingulate and orbitofrontal cortices, respectively, as shown by meta-analyses from PET and fMRI studies in perception and experience of emotion (Phan et al., 2002; Vytal & Hamann, 2010).

However, not all patients with damage in regions associated to a specific emotion appear to have the corresponding emotional deficit. For example, a patient with bilateral amygdala lesions failed to show a fear-specific impairment (Anderson & Phelps, 2000, 2002). Likewise, some patients with damage to the insular cortex have demonstrated disgust specific impairments (Adolphs et al., 2003; Calder et al., 2000), whereas others have not (Straube et al., 2010; Vianna, 2005). Finally, the only study examining sadness in patients with bilateral lesions to the subgenual ACC failed to detect any sadness impairment (Gillihan et al., 2011).

The mere fact that there are discrepancies for the aforementioned indicates that the notion of a specialised brain network underlying a specific emotion is more complex and nuanced than a simple one-to-one mapping between structure and function.

Alternatively, overlapping substrates subserving both, experience and perception of emotion may not be emotion-specific. It is certainly the case that data from patient studies (Damasio, 1994; Hornak, Rolls, & Wade, 1996; Keane, Calder, Hodges, & Young, 2002; Rolls, 1999) emphasise an important role for the frontal lobes (including the ACC) in processing emotional cues in general. For example, MacLean (1993; see also Lane, Reiman, Ahern, et al., 1997) considered emotion experience to be mediated by the ACC, Damasio (1994) has focused on the contribution of the ventromedial PFC to emotion, Rolls (1999) has posited a general role for the OFC in emotion, and others have suggested that the systems involved in coding individual emotions may feed into more general emotion systems in the frontal cortex (Sprengelmeyer, Rausch, Eysel, & Przuntek, 1998). If this is correct, we should

expect to see general impairments of emotion perception and experience following frontal cortex damage, which appears to be the case (Damasio, Tranel, & Damasio, 1990; Hornak et al., 1996; Keane et al., 2002). In support of the frontal role in emotion perception, frontal variant fronto-temporal dementia, characterised by a focused deterioration on frontal brain regions (Keane et al., 2002), has been associated with a generalised impairment for the perception of emotional expressions. Also consistent with the idea that the frontal lobe participates in the experience of emotion, orbitofrontal and anterior cingulate damage patients reported abnormal experience or exaggerated emotional responses across different emotions (Hornak et al., 2003).

Although this suggests temporal and frontal involvement across perception and experience of emotion, more subtle differences have additionally implicated right posterior regions in emotion perception and right prefrontal regions in appropriate emotional response to situations (Edwards-Lee & Saul, 1999).

1.2.1 Functional cerebral asymmetries of perception and experience of emotion

As suggested by most of studies above, the neural substrate for emotional processing has been shown to be located in the right hemisphere (e.g., Adolphs, 2002b; Adolphs et al., 2000; Belin et al., 2004; Borod, 1992; Calder, Keane, Lawrence, & Manes, 2004; Gur et al., 2002; Habel et al., 2007; Hornak et al., 1996; Phillips et al., 1998; Sabatinelli et al., 2011). This suggests that the right hemisphere is involved both in perceiving and experiencing emotions in general. However, in the attempt to dissociate between mechanisms underlying these two processes, previous studies have investigated perception and experience of emotion separately.

Functional cerebral asymmetries (FCAs) are a fundamental principle of brain organisation and a widespread phenomenon among both animals and humans, suggesting hemispheric asymmetries are evolutionary advantageous. However, only a decade from now, studies started to report FCAs in many other species, comprising vertebrates such as mammals, birds, reptiles, amphibians and fish (Gunturkun, 1997; Hopkins, 2006; Vallortigara, Rogers & Bisazza, 1999; for a review see: Rogers & Andrew, 2002; Vallortigara & Rogers, 2005). FCAs underlie dynamic changes and are rather relative than absolute (Pratt, Sinai, Laufer, & Horev, 2002; Sinai & Pratt, 2003). Based on the observation that FCAs are a widespread phenomenon, FCAs

may be the result of a selection advantage over a symmetric brain. For example, whereas one hemisphere performs certain types of computational operations, the other hemisphere executes other, different operations. When faced with complex computational problems, brains may outperform by distributing computations across the hemispheres. FCAs have also been associated with avoiding conflicts between the two hemispheres (Vallortigara, 2000), eliminating functional incompatibility between similar computations (Vallortigara et al., 1999), or increasing neural capacity (Levy, 1969, 1974, 1977). In sum, these authors agree in that the emergence of FCAs is associated with enhanced cognitive processing.

FCAs, reflecting relative differences between the two hemispheres, have been shown in humans as a fundamental principle in the brain organisation of a number of brain functions. The left hemisphere superiority is associated to speech production and perception, reading and writing, verbal memory, as well as complex and fine motor skills. The right hemisphere typically shows a relative performance advantage in, for example, visuospatial tasks, including mental rotation (e.g., Corballis, 1997), processing faces (e.g., Dien, 2009), and emotion (e.g., Ley & Bryden, 1982). Specifically, a number of emotion-related functions are represented in the right hemisphere, including the perception and expression of facial (e.g., Asthana & Mandal, 2001; Borod et al., 1998; Hugdahl, Iversen, & Johnsen, 1989; Hugdahl, Iversen, Ness, & Flaten, 1993; Mandal & Singh, 1990; Safer, 1981) and prosodic emotions (e.g., Bryden & MacRae, 1989; Grimshaw, Kwasny, Covell, & Johnson, 2003; Ley & Bryden, 1982; Shipley-Brown, Dingwall, Berlin, Yeni-Komshian & Gordon-Salant, 1988).

FCAs in facial emotion perception have been extensively documented by behavioural studies using the visual half-field paradigm (VHF; e.g., Alves, Aznar-Casanova, & Fukusima, 2009; Asthana & Mandal, 2001; Buchtel, Campari, DeRisio, & Rotal, 1978; Hugdahl et al., 1989, 1993; Safer, 1981; Ladavas, Umilta, & Ricci-Bitti, 1980; Landis, Assal, & Perret, 1979; Mandal & Singh, 1990; Strauss & Moscovitch, 1981; Suberi & McKever, 1977). The VHF-technique consists in tachistoscopically presented stimuli within left (LVF) or right visual fields (RVF) relying on the direct contralateral visual pathways from the LVF and RVF to the right and left hemispheres, respectively. Thus, although both hemispheres are involved in the processing of stimuli, the relative differences between the two

hemispheres can be examined in terms of accuracies and/or response times for stimuli presented to the LVF relative to stimuli in the RVF (see Fig. 2).

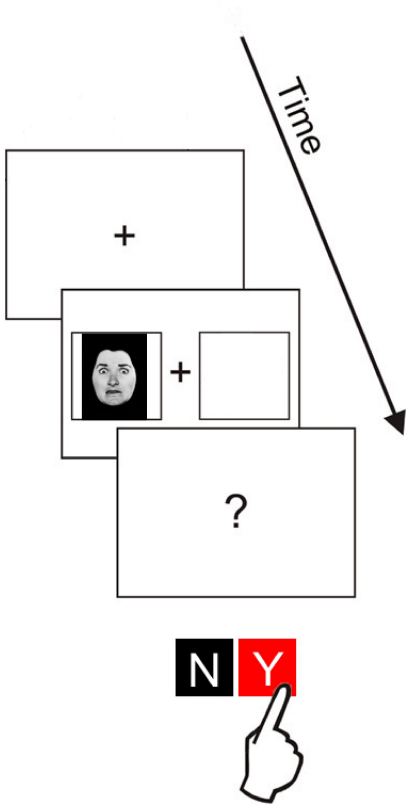

Figure 2. The visual half-field technique provides a reliable measure of functional cerebral asymmetries. Participants are seated in front of a monitor with the head fixated on a chin rest. Participants are asked to fixate a small cross in the centre of the screen during the whole experiment. Emotional faces are tachistoscopically (180 ms) presented in either the left or the right visual half-field with a stimulus eccentricity of 2–5 degree of visual angle. Due to the visual projections from the hemi-retinae of the left and right eye to the primary visual cortex of the right and left hemisphere, stimuli presented in the left visual field are primarily projected to the right hemisphere and vice versa. Participants are instructed to decide as fast and as accurately as possible whether presented is emotional (Yes) or not (No). Adapted from Bayer and Hausmann, 2011.

VHF studies have consistently shown a predominant right hemisphere role in perceiving facial expressions (e.g., Asthana & Mandal, 2001; Hugdahl et al., 1989, 1993; Mandal & Singh, 1990; Safer, 1981). Several of these studies have found higher accuracy for recognising facial expressions presented in LVF (corresponding

with the right hemisphere) than in RVF (corresponding with the left hemisphere) (e.g., Asthana & Mandal, 2001; Hugdahl et al., 1989, 1993; Mandal & Singh, 1990; Safer, 1981). Complementary findings have also shown faster responses for the perception of emotional faces presented in the LVF (e.g., Alves et al., 2009; Buchtel et al., 1978; Hugdahl et al., 1993; Ladavas et al., 1980; Landis et al., 1979; Strauss & Moscovitch, 1981; Suberi & McKever, 1977), suggesting a more efficient neural processing of emotional expression in the right hemisphere. Overall these findings lend support to the Right Hemisphere Hypothesis predicting right hemisphere superiority for the processing of emotions in general (Borod et al., 1998). According to electrophysiological and functional neuroimaging studies, the right hemisphere network underlying facial emotion perception involves temporal and posterior brain regions (Hung et al., 2010; Killgore & Yurgelun-Todd, 2007; Noesselt, Driver, Heinze, & Dolan, 2005).

However, it may be that the right hemisphere advantage results from some other factor than facial expression. For instance an alternative explanation for the aforementioned findings may be that asymmetrical patterns of eye scanning promote a right hemisphere advantage by directing greater attention to LVF than to RVF (Vaid and Singh, 1989). Evidence for this claim is provided by Heath, Rouhana, & Ghanem, (2005), who reported increased leftward biases in the perception of facial affect amongst readers of left to right scripts compared to readers of right to left scripts or bidirectional readers. Consistently, Eviatar (1997) found that right to left Hebrew readers do not exhibit a leftward perceptual bias in a chimeric happy/neutral face task. In fact, it has been shown the scanning habits or reading directions can strengthen or weaken right hemisphere superiority for facial perception (Megreya & Havard, 2011). Yet, it seems unlikely that it entirely accounts for the effect. Another potential challenge to the right hemisphere predominance in facial emotion perception is the idea that faces are processed on the basis of their configural information (Collishaw & Hole, 2000). Consistent with this indication, patients with unilateral right hemisphere lesions exhibit impaired recognition of upright faces, which would typically be processed on the basis of the configural information contained within them (Yin, 1970). In healthy participants, presentation of inverted faces results in reduced LVF advantage (e.g., Leehey, Carey, Diamond, & Cahn, 1978; Rhodes, 1993). Thus, the reported right hemisphere dominance for processing

facial emotion expression might be driven by processing configural properties of the face. However, this assumption does not explain the right hemisphere advantage for facial expressions in studies using neutral faces as a control condition (Alves et al., 2009; Christman & Hackworth, 1993; Hugdahl et al., 1988, 1993; McKeever & Dixon, 1981; Suberi & McKeever, 1977).

The right hemisphere role in emotion perception has even been extended to the auditory domain, as evidenced by studies assessing FCAs of emotional prosody. By varying task instruction, a number of studies directly compared performance on a prosodic task requiring listening for a target tone, and a linguistic task requiring participants to listen for a target word (Bryden & MacRae, 1989; Grimshaw et al., 2003; Ley & Bryden, 1982; Shipley-Brown et al., 1988; Wildgruber et al., 2005). The majority of studies looking at FCAs in emotional prosody have used the dichotic listening (DL) paradigm (Hugdahl, 1988; Kimura, 1967). This technique involves the presentation of two stimuli simultaneously (one to each ear) and requires identification of at least one of the stimuli. Results of DL studies using verbal task typically show a better reproduction of for example, spoken syllables (‘ba’, ‘ka’, ‘da’, etc.) presented via headphones to the right ear, corresponding to the left hemisphere, referred as a right ear advantage (REA; Hugdahl et al., 1999; see Fig. 3).

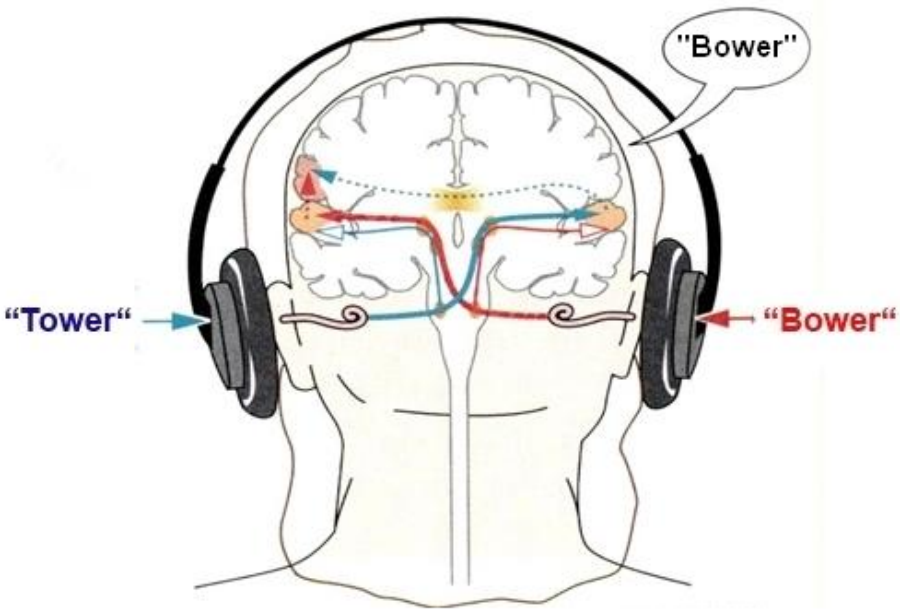

Figure 3. Schematic representation of the dichotic listening procedure using a linguistic task. Words (with happy (red) and sad (blue) tones) presented to the right ear, normally results in a better reproduction relying on preponderant projections to the primary auditory cortex of the contralateral cerebral hemisphere (highlighted in orange). Adapted from Freberg, 2006.

Left hemisphere lateralisation in language has been explained as the result of direct access to verbal stimuli presented to the contralateral right ear, whereas the information presented to the left ear has to take an indirect route involving the opposite hemisphere and the corpus callosum (Kimura, 1967). As suggested by the structural model by Kimura (1967), signals originating in each ear are projected to the primary auditory cortex of both the contra- and the ipsilateral cerebral hemisphere. However, the contralateral projections are more preponderant, resulting in a stronger representation in the contralateral hemisphere to the originating ear. Furthermore, the weaker ipsilateral pathway is presumably inhibited, thus only the input of the right ear is immediately conveyed to the left-hemisphere. Assuming that only the left hemisphere is capable to process speech, the left ear input requires interhemispheric processing via the corpus callosum. Thus, the inferior left ear performance is explained as an attenuation of information during the additional callosal relay step.

Two studies used the DL paradigm presenting intoned sentences and requiring the judgment of both, the emotional prosody and the content of the stimuli (Ley & Bryden, 1982; Shipley-Brown et al., 1988). These studies showed a left ear advantage (LEA; corresponding with the right hemisphere) for the identification of emotional prosody and at the same time an REA (corresponding with the left hemisphere) for the detection of semantic content. These findings suggest right hemisphere superiority for emotional prosody and left hemisphere superiority for verbal content of the sentence. The LEA in emotional prosody has also been found by DL studies requiring the identification of a particular tone of voice from a single word (Bryden & MacRae, 1989; Grimshaw et al., 2003). In these studies, participants were required to identify spoken words in a linguistic DL task, and emotional tone of voices in a prosodic DL task. The stimuli set for both tasks consisted of four two syllable words "bower", "dower", "power" and "tower", spoken in angry, happy, neutral and sad tones of voice. Complementary findings from neuroimaging studies have been associated with right lateralisation in temporal and frontal areas including the superior temporal and dorsolateral cortices (e.g., Buchanan et al., 2000; George et al., 1996; Imaizumi et al., 1997; Wildgruber et al., 2005). Altogether, these findings point to a right hemisphere role for the perception of emotions in both, the auditory and the visual domain.

While the aforementioned studies suggest right hemisphere involvement in emotion perception, it remains unclear whether this mechanism also underlies the recognition of emotions. For instance, how do we come to associate fearful facial expressions with the concept of fear and the perception of fear response that the stimulus triggers? Emotion recognition could involve a learned rule-based system linking configurations of perceived facial features, prosodic patterns, and body postures with the knowledge acquired about the associated experience via verbal means. According to this view there would be little if any good reason to suppose that emotion recognition is associated with the experience of emotion. By contrast, theories of "embodiment of emotion" (Niedenthal, 2007), "emotion contagion" (Leslie et al., 2004), simulation model (Buccino et al., 2001), and motor programmes (James, 1890), emphasise a link between the perception and experience of emotion. These models converge in the proposal that a capacity to experience a particular emotion (or emotions in general) underpins the recognition of that emotion (or

emotions in general). The emotional contagion account claims that perceiving another's emotional expression triggers an emotional experience in the perceiver either indirectly or via unintentional mimicry of that expression (e.g., Hatfield, Cacioppo, & Rapson, 1994; Wild, Erb, & Bartels, 2001). Alternatively, perceiving other's emotional expressions could simulate the viewed emotional state via the generation of representations of the associated body state (Adolphs, 2002) or simulated motor programmes (Carr et al., 2003; Gallese et al., 2004).

Therefore, if emotions were perceived by, for example, re-instantiating associated emotional states, the right hemispheric mechanism observed in emotion perception, should at least play some role in emotional experience. Of note, emotional experience should be understood as the occurrence of an emotional state, and thus to consist not only of certain feelings (awareness if one's emotional state) but also physiological (especially autonomic) responses. Although less extensive, evidence pointing to a right hemisphere role have also been found in emotional experience. A study in unilateral brain damage patients observed that during presentation of unpleasant films, healthy controls and left brain damage patients tended to look away, whereas right brain damage patients did not. Failure to evade the unpleasant films in the right brain damage patients was interpreted as emotional indifference and lack of emotional response (i.e., intolerance) to the stimulus (Mammucari et al., 1988).

Further evidence of a right hemisphere role in emotional experience has implicated an association with autonomic responses. For instance, several studies found impaired skin conductance responses to emotion in right brain damage patients (Morrow, Vrtunski, Kim, & Boller, 1981; Myslobodsky & Horesh, 1978; Zoccolotti, Scabini, & Violani, 1982; Zoccolotti, Caltagirone, Benedetti, & Gainotti, 1986). Complementing these findings another study implemented emotional film clips and also found impairment in the production of skin conductance in right damage patients compared to left damage patients and controls (Caltagirone, Zoccolotti, Originale, Daniele, & Mammucari, 1989). In line with the above findings of skin conductance associated with right hemisphere function, it has been proposed that the arousal component of emotional experiences is subsumed under parietotemporal regions of the right hemisphere (Heller, 1993). Supporting this

hypothesis, right parietal lesion patients show reduced skin conductance responses when presented with emotional stimuli (Heilman, Schwartz, & Watson, 1978).

As in the lesion patients, studies in healthy controls encourage a right hemisphere role in emotional experience (Wittling, 1990; Wittling & Pfluger, 1990; Wittling & Roschmann, 1993). Lateralised emotional film presentation in normal controls revealed more intense subjective emotional experience when the film was presented to the right hemisphere than to the left hemisphere (Wittling & Roschmann, 1993). Some of these studies point to a right hemisphere role in controlling and regulating fundamental bodily functions during emotional stimulation. For example, increased blood pressure was found during right compared to left hemisphere presentations of emotional films (Wittling, 1990). Another study using lateralised presentation of emotionally aversive and neutral films while assessing changes in cortisol secretion, found higher increases in cortisol when the aversive films were presented to the right hemisphere (Wittling & Pfluger, 1990). Last, VHF presentation of emotionally charged scenes and recording physiological responses suggested the involvement of the right hemisphere in inducing larger vasoconstriction responses (Spence, Shapiro, & Zaidel, 1996).

Overall these results from lesion damage patients and normal controls suggest that emotional experience is driven by a right hemisphere system particularly involved in the modulation of autonomic functions. In full agreement, William James (1980) and later Antonio Damasio (1994) have proposed that the experience of emotion mediate the perception of specific and unique patterns of somatovisceral arousal. Accordingly, experience of emotion seems to depend upon the functioning of the right parietal and right somatosensory areas (Adolphs, 2003; Adolphs & Damasio, 2000), which are considered as good candidates for a neural substrate dedicated to bodily functions.

1.2.2 Functional cerebral asymmetries in perception and experience of emotion in terms of valence

Because different emotions convey different information that is critical to survival (e.g., threat), the brain may be functionally organised according with a core feature of emotion such as valence, rather than involving processing of emotions in general. Threat-related emotions, for example, may involve a right hemisphere system

specialised for signalling danger, or harmful stimuli and preparing the organism to freeze, flee, or withdraw (Craig, 2005; Fox, 1991). This has been suggested by the finding that toads are likely to react when a predator is introduced into their monocular field projecting to the right hemisphere (Lippolis, Bisazza, Rogers, & Vallortigara, 2002). On the contrary, preferential use of the right eye projecting to the left hemisphere to categorise food from non-food has been well demonstrated in chicks (Mench & Andrew, 1986; Rogers, 1995; Zappia & Rogers, 1987).

The motivational aspect of emotion is important for integrating information about multiple changing internal states (e.g., hunger, sexual desire, or pain) and environmental conditions (including resource or reproductive opportunities, the presence of danger) that allow organising behaviour and maximising survival (Bechara, 2001). Based on the motivational attribute of emotions the Approach/Avoidance model proposes right hemisphere processing for avoidance-motivated emotions and left hemisphere processing for approach-motivated emotions (Harmon-Jones, 2004).

However, emotions also vary in terms of positive or negative valence, i.e., pleasant or unpleasant. In fact, valence differentiation of emotions has been observed in spontaneous behaviour underlying pleasant experiences, i.e., sex, food related, and unpleasant experiences, i.e., predation threat, from a variety of mammalian species including chimpanzees, mice and rats (Berridge, 1996; Berridge & Robinson, 2003). According with this attribute of emotions, the Valence-Specific Hypothesis predicts a right hemisphere dominance at mediating negative emotions and a left hemisphere dominance at mediating positive emotions (Adolphs, Jansari, & Tranel, 2001; Ahern & Schwartz, 1979; Wedding & Stalans, 1985).

Therefore, according with implications for survival and/or evolutionary advantages, emotions may be functionally organised in the brain in terms of motivation, valence or both emotional attributes. For example, one may consider that the ability to decode emotion from vocal and facial expressions involves FCAs that evolved from a specific communicated aspect of emotion, i.e., valence or motivation. However, most of the evidence rather suggests a preferential right hemisphere specialisation for the perception of emotion (e.g., Alves et al., 2009; Buchtel et al., 1976; Ladavas et al., 1980; Landis et al., 1979; Hugdahl et al., 1993; Killgore & Yurgelun-Todd, 2007; Phillips et al., 1998; Strauss & Moscovitch, 1981; Suberi &

McKever, 1977). These findings, however, might be misleading given that most of studies in emotion perception have only focussed on the Right Hemisphere Hypothesis or Valence-Specific Hypotheses, and have not directly compared the three competing models (for a more detailed discussion see Chapter 2). In fact, Chapter 2 addressing this particular question did not support any of the three competing models, revealing instead a right hemisphere advantage for negative (only) emotions.

Experience of emotion may also involve functional organisation of the brain in terms of valence. In fact, several lines of evidence have shown that valenced emotional experience is associated with differences in FCAs. One source of evidence for hemispheric asymmetries underlying emotional reaction comes from studies using the WADA technique (Perria, Rosadini, & Rossi, 1961; Rossi, & Rosadini, 1967; Terzian, & Cecotto, 1959). These studies suggest that damage in one hemisphere, releases activation within the contralateral hemisphere. This is a presurgical procedure for intractable epileptic patients consisting in unilateral intracarotid injection of amobarbital sodium. Thus, a left hemisphere involvement in negative mood including crying, pessimistic statements, and feelings of nothingness, indignity or despair has been shown in patients receiving injection into the left carotid artery. In contrast, a right hemisphere involvement in positive mood consisting in positive reactions, i.e., smiling, optimism, and overall sense of well-being, has been observed following injection into the right carotid artery. Therefore, these findings consisting in the right hemisphere eliciting depressive symptoms, and the left hemisphere positive responses, support the Valence-Specific Hypothesis in emotional experience. Similar findings have been shown by lesion studies indicating that left-sided lesions resulting from unilateral stroke are associated with dysphoric symptoms (Robinson, Starr, & Price, 1984).

Additional evidence for hemispheric asymmetries underlying emotional behaviour has been provided by Sackeim et al. (1982), conducting three retrospective studies on lateralisation of emotion regulation. A first study evaluated whether lateralised brain damage predicted valenced emotional experience. The study assessed lateralisation of brain damage in 122 cases of pathological crying and laughing. Whereas cases of pathological laughing were associated with right-sided lesions, pathological crying related to left-sided lesions. Based on the assumption

that inhibitory processes modulate emotions, the observed emotional outbursts may involve release activation within the contralateral hemisphere. A second study from Sackeim et al. (1982) similarly hypothesised that differential emotional experience depends on the side of the brain undergoing hemispherectomy, a surgical procedure resulting in virtually complete extirpation of the cortex from one hemisphere. A significant number of cases involving right hemispherectomy were associated with euphoric compared to depressive mood. Basically showing the same results as in the first study, the left hemisphere compared to right side of the brain was more consistently associated with experiencing positive mood. In a third study, Sackeim et al. (1982) investigated emotional manifestations in epilepsy frequently associated with sudden feelings of fear or terror. The study assessed lateralisation of foci in cases of ictal outbursts of uncontrollable laughing and crying. Foci of pathological laughers were more frequently associated with left-sided epileptic seizure. Cases of pathological crying were associated with right-sided epileptic seizure. These findings were in contrast with right-sided lesions in pathological laughers and left-sided lesions in patients with pathological crying. However, the emotional outbursts in epilepsy were taken as evidence of excitation in brain regions ipsilateral to the foci of ictal emotional outburst. Therefore, uncontrollable emotional reactions may either involve disinhibition, as suggested by the lesion and WADA data, or excitation, as shown in the epileptic patients.

Overall, most of these findings suggest that FCAs of emotional processing vary in terms of positive versus negative, or pleasant versus unpleasant experiences (i.e., laughing versus crying). This assumption is in line with the Valence-Specific Hypothesis and in contrast with the Right Hemisphere Hypothesis. However, none of these studies have differentiated motivational and valence aspects of emotional experience. In fact, the Approach/Avoidance model has not been directly tested given that the symptomatology of patients from these studies, i.e., pathological crying, laugher, did not reflect the motivational value of emotion.

Specifically, motivational aspects of emotion are expected to involve modulation from approach/withdrawal systems that aim to suppress interference by opposing motivational states, promote recovery of their respective motivational tendencies, and inhibit less optimal goals in favour of long-term adaptive strategies. However,

unique emotional states resulting from the balance between approach and withdrawal tendencies, and maintained by the vigilant organism may be upset.

This type of disruption can be observed in major depressive disorder (MDD) patients who exhibit a relative absence of arousal and motivation for reward, which at the extreme manifests as intentional avoidance of normally rewarding stimuli (American Psychiatric Association, 2000; Gray, 1994; Kaplan & Sadock, 1997).

In MDD, hypoactivation of the approach system leads to disinhibition in the avoidance system, involving left lateralised frontal hypoactivation and ultimately increasing avoidance behaviour (Coan & Allen, 2004). In line with an inhibited approach system, several EEG studies have shown left lateralised prefrontal activation in MDD patients (e.g., Coan & Allen, 2004; Davidson, Pizzagalli, Nitschke, & Putnam, 2002; De Raedt, Franck, Fannes, & Verstraeten, 2008; Henriques & Davidson, 1990, 1991; Jacobs & Snyder, 1996; Schaffer, Davidson, & Saron, 1983). Moreover, a recent meta-analysis found decreased left compared to right frontal cortical activation at rest in MDD patients during both depressive and euthymic states (Thibodeau, Jorgensen, & Kim, 2006). Overall these findings showing left lateralised frontal hypoactivation in MDD suggest inefficiency in the approach system for suppressing opposed motivational and affective states, maintaining avoidance and negative emotions (Tomarken & Keener, 1998). It should be noted, however, that MDD only relates to withdrawal motivation and therefore is not suitable for a more thoroughly examination of the approach/withdrawal model.

1.3. An experimental model of functional brain organisation of emotional experience

An experimental model for testing FCAs of both, valence and motivational aspects of emotional experience would be consistent with the clinical presentation of bipolar disorder (BD). BD is characterised by dysregulated emotional responses, which can eventually lead to depressive or manic mood states (Critchley, 2003; Phillips, Drevets, Rauch, & Lane, 2003). During a depressive episode BD patients typically experience depressed mood, loss of interest or pleasure in almost all activities, but also exhibit absence of arousal and motivation for reward, which at the extreme manifests as intentional avoidance of normally rewarding stimuli. In contrast, manic episodes involve a period during which BD patients experience abnormally and persistently raised, expansive, or irritable mood associated with intensified appetitive

arousal, expressed as the motivation for seeking rewarding actions of many kinds—toward pleasure, excitement, novelty, social engagement, physical risk, and social domination (American Psychiatric Association, 2000; Gray, 1994; Kaplan & Sadock, 1997). Thus, BD is related to both, valence and motivational aspects of emotion. Moreover, BD is of particular interest given that it involves the impaired ability to regulate emotions (e.g., Critchley, 2003; Morris, Sparks, Mitchell, Weickert, & Green, 2012; Phillips et al., 2003). This has been suggested by an fMRI study showing inefficient top-down inhibitory control in BD during emotional processing from negative pictures (Morris et al., 2012). In addition, euthymic BD patients have been associated with emotional hyperreactivity (M'Bailara et al., 2009), mostly evidenced in emotionally neutral situations, and more intense emotions (Henry et al., 2001, 2008).

Therefore, BD represents a useful model for investigating emotional processes and how these processes are functionally organised in the brain. Drawing from previous evidence showing that mood influences FCAs (Compton & Levine, 1997; Papousek & Schulter, 2002; Tomarken, Davidson, & Henriques, 1990; Wheeler, Davidson, & Tomarken, 1993), a key aspect of functional brain organisation, one would expect that the brain is atypically organised in BD. For example, one study revealed that FCAs across the menstrual cycle are influenced by mood state (Compton & Levine, 1997). On the basis of previous evidence showing menstrual cycle related fluctuations in FCAs (see Hausmann & Bayer, 2010, for a review), Compton & Levine, (1997) investigated the effect of mood. Assuming that menstrual cycle involves mood changes (i.e., premenstrual phase is associated with emotional lability; Yonkers, O'Brien, & Eriksson, 2008), the study tested whether FCAs vary across the menstrual cycle as a direct consequence of changes in hormone levels or because of mood changes across the cycle. However, mood in this study varied independently of cycle phase, allowing for an independent assessment of the effects of mood on FCAs. In support to a mood hypothesis, rather than a cycle-related hypothesis, results showed that dysphoric mood was associated with an atypical RVF advantage (corresponding with the left hemisphere) in a VHF face perception task. A similar mood influence on FCAs has been obtained by studies inducing positive and negative moods by using film clips (Papousek & Schulter, 2002; Papousek, Reiser, Weber, Freudenthaler, & Schulter, 2012; Tomarken et al., 1990;

Wheeler et al., 1993). For example, Wheeler et al. (1993) investigated frontal asymmetries using EEG recordings during rest (baseline) and while viewing positive and negative films eliciting happy, fearful and disgust emotions. Participants with greater relative left-sided frontal activation at baseline showed more intense negative affect compared to those showing right-sided frontal activation. Following negative films, participants with greater relative right frontal activation at baseline had more intense negative affect than participants with the opposite pattern.

In a similar way, it should be expected that FCAs (and the direction of FCAs) in BD patients also change according to their manic and depressive episodes. In line with this assumption, studies consistently reported an association between manic or depressive mood in BD and atypical FCAs (e.g., Allen, Iacono, Depue, & Arbisi, 1993; Altshuler et al., 2008; Foland et al., 2008; Harmon-Jones et al. 2002, 2008; Jogia, Haldane, Cobb, Kumari, & Frangou, 2008; Kano, Nakamura, Matsuoka, Iida, & Nakajima, 1992; Liu et al., 2012; Nusslock et al., 2012; Strakowski et al., 2011). Specifically, an electrophysiological study, for example, found higher right than left frontal activation in depressive BD patients compared to healthy controls (Allen et al., 1993). This atypical FCA is in line with findings in MDD patients showing a right hemisphere dysfunction (Coan & Allen, 2004; Davidson et al., 2002; De Raedt et al., 2008; Henriques & Davidson, 1990, 1991; Jacobs & Snyder, 1996; Schaffer et al., 1983). Complementary findings from another EEG study showed greater left lateralised prefrontal activation in manic BD patients (Kano et al., 1992). These findings are in line with studies of induced mood, supporting the Valence-Specific Hypothesis that showed that positive and negative mood corresponds with a right and left hemisphere involvement, respectively. However, it remains unclear whether FCAs in BD account for approach and withdrawal-motivated experiences.

In line with the Approach/Withdrawal model, there have been theoretical accounts linking BD to dysregulation of the behavioural approach system (BAS; Depue & Iacono, 1989; Fowles, 1993; Johnson, 2005). This system is assumed to regulate appetitive motivation and goal-directed behaviour in response to signals of reward (Gray, 2001), predicting left prefrontal asymmetry during mania. Supporting the association between enhanced approach and hypomanic BD, an increased BAS sensitivity and experiences of goal- striving and attainment events predicted future manic symptoms in BD patients (Johnson et al., 2000; Meyer, Johnson, & Winters,

2001; Nusslock, Abramson, Harmon-Jones, Alloy, & Hogan, 2007; Salavert et al., 2007).

This model has been tested by studies specifically investigating FCAs underlying approach and withdrawal-related aspects in manic and depressive BD patients (Harmon-Jones et al., 2002, 2008). According with Brehm's motivational theory (Brehm & Self, 1989; Wright, Tunstall, Williams, Goodwin, & Harmon-Jones, 1995), one study using a word scramble task with three difficulty levels (i.e., easy, medium, hard win trials) involving reward or punishment, predicted that participants would lose interest and distract when the task becomes too difficult. Whereas healthy controls followed this prediction, hypomanic BD patients were particularly responsive to challenge even when confronted with an impossible task. During the task, hypomanic BD patients also showed a left greater than right cortical EEG activation to the more demanding/rewarding task compared to healthy controls. In another study, Harmon-Jones et al. (2002) investigated FCAs in individuals with proneness to hypomanic or depressive symptoms during an anger-evoking situation, expected to elicit opposed reactance-like responses in each group. Whereas proneness to hypomanic symptoms was predicted to involve greater relative left frontal activation, proneness to depressive symptoms was expected to associate to decreased relative left frontal activation. Supporting the study's hypothesis, individuals with proneness toward hypomanic symptoms showed stronger left lateralised prefrontal activation when confronted with an anger-evoking situation. In contrast, individuals with proneness toward depressive symptoms had greater right lateralised frontal activation during an anger-evoking situation. On the one hand, the authors suggested that proneness toward hypomanic symptoms might lead to reactance-like responses, in line with increased approach (and decreased withdrawal) motivational tendencies. On the other hand, proneness toward depressive symptoms may lead to helpless responses, in line with decreased approach (and increased withdrawal) motivational tendencies, in the face of challenges. Overall, these findings showing an association between atypical FCAs and BD mood episodes, involving a left frontal asymmetry during mania and right frontal asymmetry during depression, are in line with the valence-specific, but also with the approach/withdrawal predictions. This suggests that functional brain organisation of

emotional processing (at least in BD) can be explain in terms of valence emotional experience, either in terms of approach/withdrawal or positive/negative emotions.

These findings are compatible with a BD model from Pettigrew and Miller, proposing that hemispheric imbalance (Pettigrew & Miller, 1998) predisposes to valenced styles involving either confidence, elation or mania associated with increased left hemisphere activation, or caution, apprehension or depression that are associated with increased right hemisphere activation. They argue that a deficit in interhemispheric transfer in BD arises from a dysfunctional state of interhemispheric switching, referred to as 'sticky switching' due to the abnormal slowing of the switch rate. The model proposes that acute mood episodes in BD can be explained in terms of hemispheric activation being held on the left (mania) or right (depression). The model's prediction has been supported by studies using a binocular rivalry task, reflecting competition between monocular neurons. This task requires presentation of horizontal moving grating to one eye and a vertical moving grating to the other. During this task, one hemisphere selects one of the rivalling stimuli, while the other hemisphere selects the other stimulus; therefore, competition for perceptual awareness during rivalry occurs between, rather than within, hemispheres. As predicted, euthymic BD patients revealed slowing of alternation rate during binocular rivalry compared to healthy controls (Pettigrew & Miller, 1998), which has been replicated by later studies (Nagamine, Yoshino, Miyazaki, Takahashi, & Nomura, 2009; Miller et al., 2003).

If BD involves a deficit in interhemispheric transfer, it can be expected that the corpus callosum, which normally helps equilibrating the level of activation between the hemispheres, will be especially affected. In fact, BD has been associated with pronounced abnormalities in the corpus callosum (Atmaca, Ozdemir, & Yildirim, 2007; Bearden et al., 2011; Brambilla et al., 2003). For example, BD patients compared to healthy controls showed smaller gray matter volumes in the genu, posterior body and isthmus (Atmaca et al. 2007; Brambilla et al., 2003). Moreover, another volumetric study reported shape difference marked by reduced splenium circularity in youths with BD patients compared to healthy controls (Yasar et al. 2006).

Although interhemispheric transfer could be compromised in BD given the MRI volumetric findings showing abnormalities in the corpus callosum (Atmaca et al.

2007; Bearden et al., 2011; Brambilla et al., 2003), findings from behavioural studies have not supported such claim (Bellani et al., 2010; Lohr et al., 2006). For example, depressive and manic BD patients were not significantly different from healthy controls in a consonant-vowel-consonant trigram identification task assessing interhemispheric transfer (Lohr et al., 2006). In this task, participants viewed a nonsense consonant-vowel-consonant stimulus projected to either the RVF (left hemisphere) or LVF (right hemisphere) or simultaneously to both hemispheres (bilateral condition) and were required to pronounce and spell out the syllable presented. The functional interhemispheric measure was the difference in accuracy between the bilateral condition and the better of the two hemispheres accuracy scores, with higher scores indicating more efficient interhemispheric transfer. This study revealed similarly efficient interhemispheric transfer in BD patients and healthy controls, therefore suggesting a normal interhemispheric communication in BD (Lohr et al., 2006). Similar negative findings were found by a study using a simple reaction-time task (i.e., Poffenberger task) in euthymic BD patients (Bellani et al., 2010). In this task, participants responded to visual stimuli presented either in the LVF or RVF with the right and the left hand. The crossed–uncrossed difference, in which median reaction times under the two uncrossed conditions, is subtracted from median reaction times under the crossed conditions, can be used as an estimate of interhemispheric transfer (Poffenberger, 1912). Typically, the averaged two crossed conditions yield a slower reaction time than the uncrossed conditions and this crossed–uncrossed difference is taken as a measure of callosal interhemispheric transfer time (Marzi, Bisiacchi, & Nicoletti, 1991). As in Lohr et al.'s study, BD patients did not show any significant difference in interhemispheric transfer with respect to healthy controls, again suggesting normal interhemispheric transfer in BD (Bellani et al., 2010). In sum, these behavioural findings challenge the claim that atypical FCAs in BD involve a deficit in interhemispheric transfer due to hemispheric imbalance.

Moreover, it should be noted that Pettigrew and Miller's model only considers hemispheric asymmetries for manic and depressive mood phases, but not for BD euthymia. Similarly, Harmon-Jones et al.'s theory predicts atypical right frontal asymmetries in BD depression and left frontal asymmetry during BD mania, without clear predictions for euthymia. Therefore, if the assumption of hemispheric

imbalance is true, symptom free BD patients (i.e., euthymic BD patients) should exhibit normal FCAs in contrast with the findings in symptomatic BD patients.

1.4.1. Bipolar disorder euthymia and its functional brain organisation

According to the studies above, BD involves atypical functional brain organisation regarding the valence of emotional experience, either in terms of approach/withdrawal or positive/negative emotions. However, it remains unknown whether functional brain organisation is still affected by BD regardless of mood episodes. This could be addressed by studying FCAs in BD patients during euthymic phases. Such approach also provides access to more inherent aspects of BD compared with examining acute mood phases that are influenced by ongoing symptomatology.

At this point it is worth noting the role of euthymia in BD and its relationship with mood episodes. BD involves intervals that are free of symptom interspersed by extreme manic or depressive episodes. These intervals, known as euthymia are defined as a "normal range of mood, implying absence of depressed or elevated mood" (B. J. Sadock, V. A. Sadock, & Kaplan, 2007, p. 277). Thus, it describes a state of mood when neither mania nor depression is present. When BD patients are euthymic it is indicative that their treatment is functioning correctly to alleviate their possible depressed or manic episode. According to the DSM IV (American Psychiatric Association, 2000) the pattern and sequencing of successive episodes is quite variable among patients. The duration of the euthymic interval varies from as little as a few days or weeks to as long as years or even decades. In contrast to the extreme variability of the euthymic intervals among patients, however, finding a certain regular pattern within the history of any given patient is not unusual. Indeed in some patients the euthymic interval is so regular that patients can predict sometimes to the month when the next episode will occur. Early on throughout the course of the illness, cycle length as defined as time from the onset of one episode to the onset of the next, tends to shorten. Thus, whereas the duration of the episodes themselves tends to be stable, the euthymic interval shortens, so episodes come progressively closer together. At the extreme, the interval of euthymia can even disappear, as observed in the rapid cycling BD subtype. It was Emil Kraepelin who first recorded mood episode frequencies in excess of four per year (Kraepelin, 1913).

However, the BD subtype of rapid cycling was formally proposed by Dunner and Feive (1974) based on a subset of patients who were unresponsive to lithium monotherapy and presented four or more episodes per year. In clinical and treatment studies, euthymia has usually been determined by applying rating scale cut-offs with the assumption that diminished symptoms equate to remission, which if sustained may eventuate into recovery.

In contrast to BD patients, for most individuals euthymia is the usual state. Unpleasant events cause transient dysphoria, but most people quickly return to their usual mood state. Similarly, winning a lottery makes most people very happy, but does not shift them to a permanent state of elation. Euthymia is therefore a stable state for most people—perturbations are small and the return to euthymia is invariant. Although this points to similarities between euthymia in BD and mood state of healthy subjects, it does not mean that euthymic BD patients and typical individuals still differ to some extent. For example, despite the coincidence that euthymic BD patients are not currently affected by acute mood, they are characterised by a history of mood episodes. These differences and similarities should reflect on the organisation of personality. In a dimensional perspective of BD, euthymic states would lie between 'normal mood' and acute mood as opposite extremes of a single continuum. As a consequence, studying the personality in BD euthymia allows for testing a dimensional conceptualization of BD. The majority of studies investigating personality in BD have used the Five Factor model (Costa & McCrae, 1992) which is one of the most widely used measures of "normal" dimensions of personality in psychopathology. This model is assessed with the neuroticism extraversion openness (NEO) personality inventory and comprises neuroticism, extraversion, openness, agreeableness, and conscientiousness traits (Costa & McCrae, 1992). Neuroticism and extraversion are the ones most consistently associated with psychopathology (Jabben et al., 2012; Barnett et al., 2011; Lozano & Johnson, 2001; Depue et al. 1987). While neuroticism refers to a tendency to experience negative emotions and emotional instability, extraversion is associated with social extraversion, dominance, and a tendency to experience positive emotions (Digman, 1990; Costa & McCrae, 1992). In line with the relevant role of neuroticism and extraversion in psychopathology, a personality dimension of BD has been associated with these two traits. If BD involves a dimensional

continuum, this should be reflected by deviations in these personality traits across different mood states in BD, and possibly nonclinical individuals experiencing predominant mood tendencies.

A close link between high neuroticism and depressive BD has been consistently reported (Jabben et al., 2012; Barnett et al., 2011; Lozano & Johnson, 2001). A study investigating personality traits with the Eysenck personality scale (Eysenck & Eysenck, 1975) in depressive BD patients compared to healthy controls, revealed higher scores in neuroticism (Jabben et al., 2012). Depressive episodes were also associated with increased neuroticism in a longitudinal study assessing BD patients with the NEO inventory during manic and depressive episodes and again after remission (Barnett et al., 2011). Similarly, Lozano and Johnson (2001) administered the NEO inventory to a sample of depressive BD patients and found higher neuroticism compared to normative data. Results also revealed that high neuroticism predicted depressive symptoms of BD patients with respect to their euthymic state. The link between neuroticism and depression in BD was even observed beyond clinical level. In a study which assessed a nonclinical sample, neuroticism from the NEO inventory predicted a depressive tendency, as indexed by a mood questionnaire (Murray, Goldstone, & Cunningham, 2007). Given that neuroticism is associated to negative feelings (Digman, 1990; Costa & McCrae, 1992) these findings might be restricted to depression.

However, findings of altered neuroticism in BD euthymia rather suggest a bipolarity continuum across BD phases. This has been supported by the consistent finding of increased levels of neuroticism in euthymic BD patients compared with healthy controls (Bagby et al., 1996, 1997; Barnett et al., 2011; Jabben et al., 2012; Nowakowska, Strong, Santosa, Wang, Ketter, 2005; Solomon et al., 1996; Srivastava, & Ketter, 2010). For instance, Jabben et al. (2012) found that BD patients in euthymic state scored significantly higher on neuroticism as measured with the NEO inventory, than healthy controls. Confirmation of the altered neuroticism in BD euthymia was provided by a series of studies implementing comparison with normative data (Barnett et al., 2011; Bagby et al., 1996, 1997). Further analysis from the study of Barnett et al. (2011) focussing on euthymic BD patients, revealed higher neuroticism scores relative to the score range of normative sample. In two other studies euthymic BD patients revealed significantly higher

levels of neuroticism than normative samples (Bagby et al., 1996, 1997). High neuroticism observed in depressive mood might be interpreted in terms of predisposition to negative emotions (Digman, 1990). However the results presented above show a similar pattern, although to a lesser extent, in euthymic BD patients (Lozano & Johnson, 2001) and nonclinical individuals with a depressive tendency (Murray et al., 2007) suggesting a bipolar continuum.

Alterations in personality traits have also been found in BD during manic episodes. In line with common sense associations of the adult emotional problem of mania and extraversion, it has been shown that heightened extraversive tendencies undermine manic mood (e.g., Barnett et al., 2011; Murray et al., 2007). One study suggested that the level of extraversion is strongly related to the natural variation of clinical course observed in BD, that is, extraversion was positively related to the relative frequency of manic episodes (Depue, Krauss, & Spoont, 1987). The study of Barnett et al. (2011) showed that increases in manic mood of BD patients were positively predicted by extraversion. As a human approach-related trait associated with biological mechanisms of motivation (Manufo, Yalcin, Willis-Owen, & Flint, 2008), extraversion may fuel maladaptive motivation in mania. Supporting this assumption, high novelty-seeking –an approach-related trait derived from the tridimensional personality questionnaire (Bagby, Parker, & Joffe, 1992)-, predicted first episode of mania at 6 months follow up (Strakowski et al., 1993). The evidence involving extraversion in mania has been paralleled by findings in nonclinical samples. In particular, the study by Murray et al. (2007) investigating nonclinical individuals found that a tendency to mania was positively associated to extraversion. In contrast to the high-related scores associated to manic states, normal levels of extraversion have been found in euthymic BD patients (Hirschfeld et al., 1986; Bagby et al., 1997). For instance, two studies assessing euthymic BD patients, found levels of extraversion which were comparable to normative data (Bagby et al., 1997; Hirschfeld et al., 1986). Altogether these findings suggest abnormally high extraversion in manic BD patients as well as in nonclinical individuals with manic tendencies, but normal levels of this trait in euthymic BD patients. This divergence between euthymic and manic states does not support a BD continuum associated with extraversion. Since extraversion is intimately linked to approach related behaviour, it is reasonable to expect an association with BD mania, but not with

euthymic states, possibly involving inhibition of such appetitive tendencies. However, a BD continuum became evident in neuroticism, a trait personality underlying emotion regulation (Di Simplicio et al., 2012), which may be equally disrupted across mood phases. In line with this assumption it has been shown that emotion dysregulation in BD persist throughout euthymic states (e.g., Gruber, Harvey, & Gross, 2012a; Gruber, Harvey, & Purcell, 2011; Gruber, Johnson, Oveis, & Keltner, 2008; Gruber, Purcell, Perna, & Mikels, 2012b; M'Bailara et al., 2009; Morris et al., 2012).

If BD can be understood as a continuum involving deviation in the organisation of personality, and neuroticism in particular, similar changes should be observable at the organisational level of the brain. Specifically, it is predicted that atypical FCAs in symptomatic BD patients reported in the previous section should also affect (perhaps to a lesser extent) euthymic BD patients. Most of the studies evaluating brain functioning in euthymic BD patients have used fMRI. Briefly, these studies, more thoroughly described in Chapter 5, suggest a right hemisphere dysfunction in emotional processing (e.g., Chen et al., 2010; Lee, Chen, Hsieh, Su, & Chen, 2010; Morris et al., 2012; Robinson et al., 2008; Wessa et al., 2007). However, it should be noted that conclusions on FCAs in these studies are complicated by the lack of direct statistical comparisons of bold activation between the two hemispheres. However, additional evidence for atypical FCAs has been provided by EEG studies showing right temporoparietal hyperactivation in euthymic BD patients (al-Mousawi et al., 1996; Clementz, Sponheim, Iacono, & Beiser, 1994; El-Badri, Ashton, Moore, Marsh, & Ferrier, 2001; Gyulai et al., 1997). For example, EEG during resting state showed increased activity in right temporoparietal areas in euthymic BD patients compared to healthy controls (El-Badri et al., 2001). In sum, these studies lend some support to the conclusion that BD euthymia is associated with atypical FCAs.

The assumption that FCAs are affected by mood episodes has been strongly supported by the studies above on symptomatic BD patients as well as studies on healthy controls. So far, only a few studies investigated FCAs in emotion processing in euthymic patients. The idea of atypical FCAs in BD euthymia, however, would be consistent with the suggestion of a BD continuum as shown by the findings of abnormally high neuroticism across mood phases. Given that this particular personality trait has been associated with emotion dysregulation (Di Simplicio et al.,

2012), atypical FCAs in euthymic BD patients, if present, may relate to emotional processing. To resolve this discrepancy, Chapter 5 investigates the hypothesis that BD euthymia involves atypical FCAs, possibly underlying emotional dysregulation, by testing emotional prosody in symptom free BD patients using a DL task.

Given that the dimensional continuum in BD linked to neuroticism was also observed in nonclinical samples with a mood tendency, the atypical functional brain organisation affecting the right hemisphere might also extend towards the healthy population at large. This implies an atypical functional brain organisation even at the lower end of the spectrum of personality traits associated with BD.

BD patients typically exhibit impaired capacity to produce and regulate appropriate affective responses (Critchley, 2003; Morris et al., 2012; Phillips et al., 2003). Consistent with this assumption a recent study has shown a failure to adapt to emotional stimuli and showed a right greater than left baseline asymmetry in the ventrolateral frontal cortex (Papousek et al., 2012). Papousek et al. (2012) examined these abilities also in healthy controls to investigate whether FCAs at baseline predicted adaptive responses to affective challenges. EEG asymmetry patterns were recorded at baseline and again during auditory induced positive (i.e., cheerful) and negative (i.e., sad) affective states. Participants were subdivided in two groups based on their baseline asymmetry in ventrolateral frontal areas. A left greater than right activation pattern at rest was associated with a shift towards the right during negative clips, and a shift to the left during positive stimulation. It was concluded that the variation of the phasic responses in individuals with a left greater than right asymmetry across the consecutive sound clips reflected more effective affective flexibility as compared to individuals with a right greater than left asymmetry. In fact, participants with a right greater than left activation pattern at baseline appeared unresponsive to both sound clips. This finding parallels findings in euthymic BD patients showing hyperreactivity (M'Bailara et al., 2009; Morris et al., 2012) and emotion dysregulation (Critchley, 2003; Morris et al., 2012; Phillips et al., 2003) as well as atypically increased right ventrolateral frontal response to emotional stimuli (Morris et al., 2012).

Thus, these findings leave the open question whether atypical FCAs underlying BD across a continuum dimension are also observed at the lower end of the spectrum. This presumption will be addressed in Chapter 3 by using a prosodic DL

task in healthy participants with a hypomanic-related personality trait, thereby testing whether right hemisphere dysfunction in emotional processing can be already found in the healthy BD spectrum.

1.4.2. A generalised right hemisphere dysfunction in bipolar disorder euthymia

Other methods for assessing brain lateralisation are given by measures of handedness and hand preference (i.e., relative hand skill). The 'right shift' model from Annett (1985) has explained the predominance of right-handers (with a left shift in hemisphere dominance) in humans in terms of genetic predisposition that controls the neurodevelopmental process of brain lateralisation. Exceptional cases involving a more bilateral representation of handedness, as observed in schizophrenia, may result from a failure to develop and sustain a normal hemispheric lateralisation (Gur, 1999). Following this view, Savitz, van der Merwe, Solms, & Ramesar, (2007) assessed handedness, footedness, and relative hand skill in euthymic BD patients, and their affected and unaffected relatives. Hand skill was assessed with the relative hand skill test consisting of a series of circles arranged in repeated pattern. Here, subjects were required to make dots inside the circles following the pattern. BD patients were significantly more lateralised in handedness, footedness, and relative manual dextrality, indicating an over-accentuated left hemisphere dominance. The authors interpreted this finding as evidence for excessive left hemisphere dominance, with a right hemisphere concomitant dysfunction in mood regulation, predisposing to depressive or manic episodes. However, hand-related measures that provide an indirect assessment of lateralisation, are unrelated to emotional processes. Therefore the authors' assumption of atypical FCAs involving the right hemisphere in mood dysregulation remains highly speculative without additional assessment of emotional processing.

A better interpretation is that the right hemisphere dysfunction affects BD euthymia regardless of emotion processing. In fact, a number of neuroimaging studies in BD have repeatedly shown a right hemisphere involvement in non-emotional processes such as working memory and sustained attention (e.g., Brooks, Bearden, Hoblyn, Woodard, & Ketter, 2010; Lagopoulos, Ivanovski, & Malhi, 2007; Monks et al., 2004; Townsend, Bookheimer, Foland-Ross, Sugar, & Altshuler, 2010). A right hemisphere deficit in non-emotional functions have been shown by a

number of fMRI studies showing reduced right hemisphere activation in dorsolateral PFC and parietal regions in euthymic BD patients (Lagopoulos et al., 2007; Monks et al., 2004; Townsend et al., 2010). One study, for example, used an n-back task presenting a sequence of stimuli that requires detecting a stimulus that appeared two positions back (Townsend et al., 2010). Euthymic BD patients showed significantly less activation than controls in right frontal and right parietal regions when participants performed the n-back task. In another fMRI study investigating euthymic BD patients, the right hemisphere dysfunction was associated with processes involved in sustained attention (Brooks et al., 2010). The study used a continuous performance task, involving presentation of letters in the centre of the screen that requires button press, unless the letter X occurs. An atypical hypoactivation of right frontal areas was strongly related to commission errors in BD patients compared to healthy controls.

However, right hemisphere dysfunction in euthymic BD patients may not only relate to one specific cognitive process (i.e., attention, working memory) but to non-emotional processes in general. Frantom et al. (2008) tested this assumption using a neuropsychological test battery in euthymic BD patients. The neuropsychological battery included tests from different cognitive domains such as executive functions, attention/processing speed, verbal learning and memory, and working memory. Laterality effects were examined by calculating composite scores for tasks associated with right and left hemisphere functioning. Euthymic BD patients demonstrated significantly lower performance in right composite scores compared to healthy controls. Also, right compared to left cognitive composites were significantly different in BD patients but not in healthy controls. The findings were interpreted as a general right hemisphere deficit in BD patients. Although these findings suggest that BD patients show impaired cognitive performance related with the right hemisphere, the composite scores used by Frantom et al. are a very indirect laterality measure, and therefore complicates the conclusion of atypical FCAs. Overall these findings suggest a general right hemispheric dysfunction in BD euthymia also affecting mental processes of the right hemisphere that are not related to emotion. However, none of the studies above directly assessed FCAs using a reliable laterality measure. Therefore, to thoroughly examine a general right hemisphere dysfunction, Chapter 6 investigates FCAs in euthymic BD patients using

the visual line bisection task–a test that typically reveals right hemispheric dominance in allocating visuospatial attention.

If BD is associated with atypical FCAs independent of acute mood episodes, the brain organisation in this condition may be sustained by intrinsic mechanisms. Such functional brain organisation would be consistent with dysfunctions such as emotion dysregulation and or hypereactivity, which have been shown to persist throughout mood phases (e.g., Gruber et al., 2008, 2011, 2012a, 2012a; M'Bailara et al., 2009; Morris et al., 2012). For instance, elevated emotional responses, defined as *emotional reactivity* (Johnson, 2005), have been found in euthymic BD patients (M'Bailara et al., 2009). This was investigated by a study using an emotional induction technique consisting in the presentation of emotional pictures followed by subjective and objective evaluation. Specifically, BD patients exhibited higher levels of emotional reactivity in response to neutral and emotional images compared to healthy controls. The findings were suggestive of a potential candidate phenotype and/or risk factor, involving emotional reactivity, for BD. Investigating symptom free BD patients while not engaged in any psychological process may identify the neural substrate of such candidate phenotype. Chapter 4 investigates this question applying functional connectivity analysis of the amygdalae with other brain regions during resting fMRI in euthymic BD patients compared to healthy controls.

1.5. Summary

There is substantial evidence that the right hemisphere is predominantly involved in the perception and experience of emotions. However, emotions are complex involving differences in valence and motivation with implications for survival and/or evolutionary advantages. Thus, the hypothesis that the right hemisphere processes all emotions does not explain a more complex functional brain organisation required to process these specific aspects of emotions and therefore involving more specialised mechanisms. The influence of valence in functional brain organisation, particularly in emotional experience is supported by findings of an impact of mood on FCAs. BD, involving manic and depressive mood episodes, is an ideal clinical model for studying FCAs of both, valence and motivational aspects of emotional experience. In line with a valenced processing of emotions, atypical FCAs in BD, involves a left frontal asymmetry during mania, and right frontal asymmetry during depression.

Although less clear, there have been suggestions of atypical FCAs in symptom free BD patients, particularly involving right hemisphere dysfunction in emotional processing. Importantly, if atypical FCAs were confirmed in BD euthymia, BD models arguing a hemispheric imbalance on the basis of acute mood episodes would be especially challenged. The atypical FCAs may also affect BD at a lower spectrum, which has been suggested by previous findings in healthy controls showing a failure to adapt to emotional stimuli and atypical right greater than left baseline frontal asymmetry. BD may also involve atypical functional brain organisation irrespective of emotional processing. It has been suggested that a right hemisphere dysfunction in euthymic BD patients affects non-emotional psychological processes. Moreover, atypical FCAs in BD may be sustained by emotional deficits such as emotion dysregulation that persists trough out mood episodes. If such FCAs were confirmed, one would expect that default networks underlie the functional brain organisation of BD.

1.6. Aim of the present thesis

The aim of the present thesis is to answer three major questions. First, the present thesis aims to investigate FCAs in emotion perception in a healthy population, thereby reevaluating empirical evidence with respect to the three partly conflicting models of FCAs in emotion perception: the Right Hemisphere Hypothesis, the Valence-Specific Hypothesis, and Approach-Withdrawal model. In order to do so, the VHF technique has been used to investigate FCAs in emotional face perception (Chapter 2). The following chapter (Chapter 3) investigates whether symptom free individuals at the lower spectrum of BD involve atypical FCAs in emotional processing using a DL task. Individuals with high hypomanic related traits were expected to show similar atypical functional brain organisation as euthymic BD patients.

The second part of my thesis looks at FCAs in euthymic BD patients. First, FCAs in default networks were investigated by a resting state fMRI study (Chapter 4) applying functional connectivity in the amygdala network in euthymic BD patients. The results are analysed with the Granger causality analysis in order to assess the expected afferent and efferent influences of an atypical amygdala network in BD. Second, emotion perception in euthymic BD patients (Chapter 5) was investigated

with a prosodic DL task assessing FCAs. We predicted that euthymic BD patients would be associated with a reduced right hemisphere advantage particularly in emotional prosody. Finally, FCAs in terms of a cognitive process which is well-known to reflect RH functioning, albeit unrelated to emotional processing was assessed in BD using a visuospatial attention task (Chapter 6). In line with a generalised right hemisphere dysfunction, symptom free BD patients were predicted to show atypical FCAs.

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Chapter 2

For over more than four decades, studies have shown that FCAs play a part in the perception of emotions, repeatedly implicating right hemisphere processing (e.g., Buchtel, Campari, DeRisio, & Rotal, 1978; Burton & Levy, 1989; Hugdahl, Iversen, Ness, & Flaten, 1989; Hugdahl, Iversen, & Johnsen, 1993; Jansari, Rodway, & Goncalves, 2011; McKeever & Dixon, 1981). However, it is still unclear whether the organisation of the brain underlying emotional processing varies according to specific attributes of emotion (e.g., Jansari et al., 2011; Rodway, Wright, & Hardie, 2003; Stafford & Brandaro, 2010). Yet, available models on FCAs have not been fully examined, as previous studies did not directly contrast FCAs in terms of individual emotions, broad categories and emotion in general. To address this question the present study investigates FCAs for emotion perception in terms of valence, individual emotions, and motivational value.

Since perceiving another's emotional expression triggers an emotional experience in the perceiver (e.g., Hatfield, Cacioppo, & Rapson, 1994; Wild, Erb, & Bartels, 2001), finding a general principle of evaluative processing of emotions, should also have implications for explaining the brain organisation of emotional experience. As emotional experience finds an experimental model in BD, revealing specific patterns of FCAs would provide with a testable model of the brain organisation of BD. However, such general principles underlying emotion perception in healthy individuals shall especially overlap with the brain organisation of euthymic BD patients, as euthymia is the closest stable state to usual mood in most people.

Models of hemispheric specialization in facial emotion perception – a reevaluation

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Abstract

A considerable amount of research on functional cerebral asymmetries (FCAs) for facial emotion perception has shown conflicting support for three competing models: (i) the Right Hemisphere Hypothesis, (ii) the Valence-Specific Hypothesis, and (iii) the Approach/Withdrawal model. However, the majority of studies evaluating the Right Hemisphere or the Valence-Specific Hypotheses are rather limited by the small number of emotional expression used. In addition, it is difficult to evaluate the Approach/Withdrawal hypothesis due to insufficient data on anger and FCAs. The aim of the present study was (a) to review visual half field (VHF) studies of hemispheric specialization in facial emotion perception and (b) to reevaluate empirical evidence with respect to all three partly conflicting hypotheses. Results from the present study revealed a left visual field (LVF)/right hemisphere advantage for the perception of angry, fearful, sad, and surprise facial expression and a right visual field (RVF)/left hemisphere advantage for the perception of happy expressions. Thus, FCAs for the perception of specific facial emotions do neither fully support the Right Hemisphere Hypothesis nor the Valence-Specific Hypothesis or the Approach/Withdrawal model. A systematic literature review, together with the results of the present study, indicate a consistent LVF/right hemisphere advantage only for a subset of negative emotions which included anger, fear and sadness, rather suggesting a "negative (only) valence model".

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Introduction

There has been considerable evidence supporting the idea that the left and the right hemispheres are differentially involved in the perception of emotions (Adolphs, Jansari, & Tranel, 2001; Ahern & Schwartz, 1979; Harmon-Jones, 2004; Wedding & Stalans, 1985), which is relatively consistent across different cultures (Eviatar, 1997).

However, far from been unanimous, studies on FCAs for facial emotion perception have led to three partly conflicting models: (i) the Right Hemisphere Hypothesis (Borod et al., 1998), (ii) the Valence-Specific Hypothesis (Adolphs et al., 2001; Ahern & Schwartz, 1979; Wedding & Stalans, 1985), and (iii) the Approach/Withdrawal model (Harmon-Jones, 2004). The first hypothesis posits that all emotions are preferentially processed by the right hemisphere. The second, Valence-Specific Hypothesis proposes left hemisphere specialization for processing positive emotions (e.g., happiness, surprise) and right hemisphere dominance for processing negative emotions (e.g., anger, fear, disgust, sadness). Finally, the Approach/Withdrawal model, considered as another version of the Valence-Specific Hypothesis, proposes that FCAs are organised according to approach and withdrawal motivation (Harmon-Jones, 2004). Approach motivation is related to a drive of the individual toward the environmental stimuli which has been proposed to be primarily processed by the left hemisphere. On the other hand, withdrawal behaviours leading the individual away from the environment are associated with right hemisphere processing. The two versions of the Valence-Specific Hypothesis overlap with respect to the majority of emotions. However, both versions differ substantially with respect to anger. Whereas the original Valence-Specific Hypothesis considers anger as a negative emotion arising from events that are unpleasant or undesired (Harmon-Jones, 2004), the Approach/Withdrawal Hypothesis categorizes anger as an approach tendency because it implies a goal blockage disruption (Berkowitz, 1993; Depue & Zald, 1993). Therefore anger has crucial implications for differentiating between the two versions of the Valence-Specific Hypothesis. FCAs in valence-specific processing have also been reported in other species, suggesting a possible evolutionary adaptive principle. For example, in rats the right hemisphere controls fear responses (Robinson, 1985) and a right eye and left hemisphere guidance is

involved in prey-catching in a wide variety of birds species, but also fishes, reptiles and toads (MacNeilage, Rogers, & Vallortigara, 2009). Although the Approach/Withdrawal model directly relates to emotional experience, it is possible that facial emotion perception might activate neural networks that are associated with emotional experience. This might particularly be the case for the amygdala which has been associated with greater right compared to left-sided activation during LVF presentation of fearful faces (Noesselt, Driver, Heinze, & Dolan, 2005; Hung et al., 2010). If FCAs for facial emotion perception depend on motivational direction, then one would expect a left hemisphere advantage for happiness, surprise, and anger (approach motivation), and a right hemisphere advantage for sadness, fear and disgust (withdrawal motivation).

The right hemisphere and the valence-specific models in facial emotion perception have been evaluated by a large number of studies using the VHF technique (Alves, Aznar-Casanova, & Fukusima, 2009; Buchtel et al., 1978; Burton & Levy, 1989; Hugdahl et al., 1989, 1993; Jansari et al., 2011; Landis, Assal, & Perret, 1979; Ley & Bryden, 1979; McKeever & Dixon, 1981; Reuter-Lorenz & Davidson, 1981; Rodway et al., 2003; Safer, 1981; Stafford & Brandaro, 2010; Strauss & Moscovitch, 1981; Suberi & McKeever, 1977; van Strien & van Beek, 2000). The VHF paradigm is an experimental technique that relies on the visual projections from the right and left hemiretina of the eyes to the right and left cerebral hemispheres, respectively. Thus, an emotional face briefly presented in the LVF is finally projected to the contralateral right hemisphere and vice versa. Although both hemispheres are involved in emotional processing, the relative differences in emotional face perception can be detected by differences in accuracy and/or response times for emotional faces presented in the LVF (corresponding to the right hemisphere) relative to the performance following RVF (corresponding to the left hemisphere) stimulation. Among the studies evaluating both left and right handers (e.g., Rodway et al., 2003; van Strien & van Beek, 2000), no differences in FCAs for facial emotion perception have been reported, suggesting that right hemisphere advantage in facial emotion perception is relatively independent from handedness.

Although FCAs are measured under experimental conditions such as the VHF paradigm, fMRI studies investigating the functional brain organisation almost always report FCAs in brain activation following foveal presentation of emotional stimuli (e.g., Blair, Morris, Frith, Perrett, & Dolan, 1999; Gauthier, Behrmann, &

Tarr, 1999; Morris et al., 1998). Similar FCAs have been found in other modalities, for example in a dichotic listening task which required participants to recognize a particular emotional tone of voice (e.g., Grimshaw, Kwasny, Covell, & Johnson, 2003). Given that FCAs in emotion perception can be observed across modalities, this suggests a general mechanism in the functional brain organisation for emotion processing.

Several of these VHF studies have shown results favouring the Right Hemisphere model in facial emotion perception (Alves et al., 2009; Buchtel et al., 1978; Hugdahl et al., 1989, 1993; McKeever & Dixon, 1981; McLaren & Bryson, 1987; Landis et al., 1979; Ley & Bryden, 1979; Safer, 1981; Strauss & Moscovitch, 1981; Suberi & McKeever, 1977). Specifically, Safer (1981) revealed higher accuracy rates for recognizing facial emotions presented in the left visual field (LVF) using the six basic emotions. Similarly, Alves, Aznar-Casanova, and Fukusima, (2009) tested five groups of healthy controls with an assigned emotional target of happy, surprise, fearful, sad or neutral expression and asked participants to indicate the VHF where the target was presented. Alves, Aznar-Casanova, and Fukusima, (2009) found faster responses to LVF presentations only for happy and fearful faces but not for sad and surprise stimuli. However, the authors interpreted their finding as support for the Right Hemisphere Hypothesis (Alves et al., 2009). Likewise, a series of other studies, found faster responses and/or higher accuracy for the perception of emotional faces presented to the LVF. Although these studies only included three (Landis et al., 1979; McKeever & Dixon, 1981; Strauss & Moscovitch, 1981; Suberi & McKeever, 1977) or two emotions (Buchtel et al., 1978; Hugdahl et al., 1993; McLaren & Bryson, 1987), the results were interpreted as support for the Right Hemisphere Hypothesis.

Moreover, the evidence is additionally limited by the fact all these studies used different paradigms including the match-to-sample, emotion recognition, and same-different paradigms. Moreover, the majority of studies did not differentiate between specific emotions but analysed them in combination, which makes it difficult to evaluate whether the valence hypotheses are perhaps the better approach. The study of Alves, Aznar-Casanova, and Fukusima, (2009) is one of the few VHF studies that differentiated between positive and negative emotion perception. However, their results clearly favouring the Right Hemisphere Hypothesis were restricted to happy and fearful emotions. Moreover, with only a few exceptions (e.g., Alves et al., 2009),

the majority of studies reporting a general right hemisphere advantage did not include neutral faces as a control condition. Therefore it cannot be ruled out that a general right hemisphere superiority for emotional face processing was promoted by a general right hemispheric advantage for face processing. In fact, there is extensive evidence from VHF studies, functional neuroimaging, and studies on patients with right hemispheric lesions (e.g., Bentin & Deouell, 2000; Bourne & Hole, 2006; Marotta, McKeeff, & Behrmann, 2002) that the right hemisphere is dominantly involved in face perception regardless of the emotional valence of the face stimuli.

As already mentioned above, there is also evidence supporting a differential involvement of the two hemispheres in processing specific emotions in terms of valence (e.g., Jansari et al., 2011; Rodway et al., 2003; Stafford & Brandaro, 2010). There are three studies that found a valence-specific laterality effect with a LVF advantage for negative emotions and a RVF advantage for positive emotion corresponding to the right and left hemisphere, respectively (Jansari et al., 2011; Rodway et al., 2003; Stafford & Brandaro, 2010). These three studies used facial expressions of the six basic emotions, presented simultaneously in the left and right VHF with an emotion label presented centrally and above the faces. Participants were asked to identify the emotional face matching the label (Jansari et al., 2011; Rodway et al., 2003; Stafford & Brandaro, 2010). In Stafford and Brandaro (2010), the valence-specific laterality finding was restricted to ‘surprise’ and ‘anger’, considered as positive and negative emotions, respectively. A similar valence-specific laterality effect, with faster reaction times for negative emotions in the LVF and positive emotions in the RVF was reported by a VHF study that used the four specific emotions of sadness, delight, anger and content (Burton & Levy, 1989). Finally, other VHF-studies found faster responses to happy and sad emotions presented to the RVF and LVF, respectively; but no further emotions were included (Davidson, Mednick, Moss, Saron, & Schaffer, 1987; Reuter-Lorenz & Davidson, 1981; Reuter-Lorenz, Givis, & Moscovitch, 1983).

Although some of these studies partly support the Valence-Specific Hypothesis evaluating the six basic emotions (Jansari et al., 2011; Rodway et al., 2003; Stafford & Brandaro, 2010), all of them used a task which asks participants to match emotional facial expressions to a verbal label and thus it cannot be ruled out that hemispheric specialization for emotional face processing was confounded by language. Consequently the valence-specific laterality effect might be confounded

by preferential involvement of the language-dominant left hemisphere. Regardless of this limitation, the only study analysing FCAs for six basic emotions found a valence-specific effect only for surprise and anger (Stafford & Brandaro, 2010). The remaining VHF studies supporting the Valence Specific-Hypothesis used a smaller number of specific emotions and found that only the perception of happy and sad emotions supported the valence model (Davidson et al., 1987; Reuter-Lorenz & Davidson, 1981; Reuter-Lorenz et al., 1983). Considering the above mentioned limitations of all these studies, the claim that FCAs for facial emotion perception account for the Valence-Specific model might be compromised.

The majority of studies examining the Approach/Withdrawal Hypothesis in normal participants have focused on the experience or expression of emotion (e.g., Davidson, Ekman, Saron, Senulis, & Friesen, 1990; Davidson & Fox, 1982). To the best of our knowledge only one recent study has examined the Approach/Withdrawal model for perception of emotional faces in normal participants (Alves et al., 2009). Five groups of healthy controls were tested with an assigned emotional target of happiness, sadness, surprise, fear, or neutral (Alves et al., 2009). The study used an emotion recognition task presenting two facial expressions, one emotional and one neutral in either visual field. Participants were asked to identify the side of the emotional target. The analyses for specific facial expressions showed shorter response times for happy and fearful expressions in the LVF, but no VHF effect for surprise or sad expressions. Interestingly, Alves, Aznar-Casanova, and Fukusima, (2009) also found shorter response times for neutral faces presented in the RVF. In particular the finding of a LVF advantage and the lack of FCAs for the perception of fearful and sad faces, respectively, did not support either of the valence hypotheses. Moreover, the Approach/Withdrawal model could not be assessed due to the lack of angry faces, the only emotional expression that allows differentiating between both versions of the valence hypotheses. Although support for the Right Hemisphere Hypothesis was assumed on the basis of the LVF advantage for happy and fearful expressions, this finding does not fully support the model's prediction of a right hemisphere processing for all emotions.

As discussed above, the majority of studies evaluating the Right Hemisphere or the Valence-Specific Hypotheses are rather limited by the small number of emotional expression used. Additionally, not enough data is available on anger and FCAs, which makes it difficult to decide whether the Approach/Withdrawal

hypothesis might account for FCAs in emotion perception. The present VHF study aims to test all three partly conflicting hypotheses by presenting Ekman-Friesen faces of all six basic emotions (and emotionally neutral faces).

Methods

Participants

Fifty neurologically healthy participants (25 women, 25 men) participated in this study. The mean age for women was 29.56 years (SD = 3.22, range: 25–35 years) and 30.44 years (SD = 3.44, range: 25–36 years) for men. Ethnicity of all 50 participants was Caucasian (i.e., the same as the emotional faces used by Ekman and Friesen (1976). All participants were right-handed, as determined by the Edinburgh Handedness Inventory (EHI; Oldfield, 1971). The laterality quotient (LQ) provided by this test is calculated as LQ = [(R − L)/(R + L)]/100, resulting in values between −100 and +100. Positive values indicate right-handedness, while negative values indicate left-handedness. Women had a mean LQ of 88.31 (SD = 12.86), while men had a mean LQ of 89.45 (SD = 12.98). There was no sex difference in age, LQ, or years of education (all $t < .93$, n.s.).

All participants had normal or corrected to normal visual acuity and were naïve as to the experimental hypotheses. Participants included students and members of staff who were recruited by announcements and were paid for their participation.

Emotional Faces Task

Emotional faces were taken from the Pictures of Facial Affect Series (Ekman & Friesen, 1976). The images were black and white and measured 313 pixels x 402 pixels. Faces of men and women with neutral expression and expressions of six basic emotions (anger, disgust, fear, happiness, sadness and surprise) were showed. For each emotion, 12 pictures, being 4 males and 4 females (4 repeated posers: 2 males and 2 females), were presented in each visual half field, comprising 12 stimuli for each emotion and 72 for all emotions. Neutral expression comprised 72 stimuli. The stimuli were presented in a counterbalanced order for poser, emotion, and visual half field.

Participants were asked to place their head on a chin rest, at a distance of approximately 57 cm from a monitor, so that 1 cm represents 1° visual angle. To ensure that lateralised stimuli were presented 2.2° visual angle to the left or right of a central fixation cross, participants were instructed to keep their head and body still and to fixate the fixation cross during the whole experiment. All stimuli were presented tachistoscopically for 180 ms in a frame of 3.9 cm width and 5.1 cm height (3.3° and 4.3° visual angle, respectively) with an interstimulus interval of 2 s. The experimental task took about 11 minutes and was run on a standard PC with an Intel Celeron Processor (2 GHz) and a standard 19-inch CRT monitor (Dell, D1226h) operating with a refresh rate of 60 Hz.

Participants were asked to indicate as quickly and correctly as possible whether the presented stimuli showed an "emotional" or "emotionally neutral" face. A trial started with a 2 s presentation of a central fixation cross. Then the stimulus was displayed in the LVF or RVF (in a pseudo-randomised order), while an empty frame appeared simultaneously in the contralateral VHF. Subsequently, participants had to indicate by button press ("Yes" or "No") whether the stimulus was an emotional or neutral face. Two hundred and ninety eight trials were employed by this procedure, the first 10 practice trials were excluded from the analysis. After 144 trials the responding hand was changed in a balanced order. Accuracy (hit rates) and response times (RTs) for correct responses were measured for each VHF.

Results

VHF Emotional Faces Task

Hit rates and median RTs were submitted to a 2 x 2 x 2 analysis of variance (ANOVA), with Emotion (emotional/neutral) and VHF (LVF/RVF) as within-participants factors and Sex as between-participants factor. Geenhouse-Geisser procedure was used with epsilon-corrected degrees of freedom, if data showed significant deviations from sphericity. In case of significant interactions, alpha-adjusted (Bonferroni) posthoc *t*-tests were performed. To avoid inflation of Type I error for multiple comparisons, significance levels was set to $p = .01$.

Right Hemisphere Hypothesis

To test the Right Hemisphere Hypothesis, facial expressions were grouped according to emotional (sadness, anger, disgust, fear, surprise and happiness), and neutral expressions. The 2 x 2 x 2 ANOVA with Emotion (emotional/neutral) and VHF (LVF/RVF) as within-participants factors and Sex as between-participants factor revealed a significant main effect of Emotion, $F(1, 48) = 24.39$, $p < .001$, $\eta^2 = .34$, with higher hit rates for the emotional faces than for neutral faces. The interaction between Emotion and VHF was also significant, ($F(1, 48) = 12.30$, $p < .001$, $\eta^2 = .20$). Paired *t*-tests revealed a significant LVF advantage for emotional faces ($t(49) = 4.53$, $p < .001$), but no VHF differences for neutral faces ($t(49) = -1.45$, n.s). Moreover, there were higher accuracies for emotional compared to neutral faces in the LVF ($t(49) = 6.25$, $p < .001$), but not in the RVF ($t(49) = 1.99$, n.s.).

In the corresponding analysis for median RTs, the main effect of Emotion was significant, $F(1, 48) = 16.64$, $p < .001$, $\eta^2 = .26$, with faster responses for emotional than for neutral faces. There was also a main effect of VHF, $F(1, 48) = 7.70$, $p < .01$, $\eta^2 = .14$, with faster responses to faces presented in the LVF compared with the RVF. The interaction between Emotion and VHF was not significant ($F(1, 48) = 3.48$, n.s.).

Both analyses (hit rates and response times) did not reveal any significant effects involving Sex (all $F < 2.92$, n.s.). Mean hit rates and RTs to emotional and neutral facial expressions for each VHF are presented in Table 1.

		LVF	RVF
Hit rates	Emotion	90.78 ± 6.37	86.67 ± 7.40
	Neutral	81.22 ± 9.40	83.44 ± 8.89
RTs	Emotion	880.6 ± 167.6	919.8 ± 179.8
	Neutral	1041.6 ± 272.7	1045.8 ± 322.9

Table 1. Mean hit rates and RTs (M ± SD) to emotional and neutral facial expressions presented in the left visual field (LVF) and right visual field (RVF).

Valence Hypothesis

To test the original Valence Hypothesis, hit rates were subjected to a 2 x 2 x 2 ANOVA, with Valence (positive/negative) and VHF (LVF/RVF) as within-participants factors and Sex as between-participants factor. Trials with neutral faces were excluded. The analysis revealed a significant main effect of Valence, $F(1, 48) = 61.63$, $p < .001$, $\eta^2 = .56$, with higher hit rates for positive emotions, than for the negative emotions. The main effect of VHF was also significant, ($F(1, 48) = 10.29$, $p < .005$, $\eta^2 = .18$), indicating a LVF advantage. Moreover, the interaction between VHF and Valence was significant, $F(1, 48) = 36.46$, $p < .001$, $\eta^2 = .43$. Simple comparisons revealed a significant LVF advantage for negative emotions, ($t(49) = 6.28$, $p < .001$), but no VHF differences for the positive emotions ($t(49) = -.60$, n.s.).

In the corresponding analysis for median RTs, the main effect of Valence was significant, ($F(1, 48) = 34.93$, $p < .001$, $\eta^2 = .42$), again indicating faster responses for positive emotions. The main effect of VHF was also significant ($F(1, 48) = 12.34$, $p < .001$, $\eta^2 = .20$), indicating an advantage for faces presented in the LVF compared with the RVF. The interaction between Valence and VHF was not significant, ($F(1, 48) = 2.49$, n.s.). Mean hit rates and RTs (M ± SEM) to positive and negative facial expressions for each VHF are presented in Table 2.

Both analyses (hit rates and response times) again did not reveal any significant effects involving Sex (all $F < 1.43$)

		LVF	RVF
Hit rates	Positive	93.50 ± 6.08	94.17 ± 6.42
	Negative	89. 42 ± 8.26	82.92 ± 8.90
RTs	Positive	848.4 ± 162.9	875.4 ± 186.8
	Negative	896.6 ± 175.1	942.0 ± 183.0

Table 2. Mean hit rates and RTs (M ± SD) to positive and negative facial expressions presented in the left visual field (LVF) and right visual field (RVF).

Approach/Withdrawal Hypothesis

To test the Approach/Withdrawal Hypothesis, emotions were grouped according to approach motivated emotions (happiness and anger) and withdrawal motivated emotions (disgust, fear, sadness and surprise), the 2 x 2 x 2 ANOVA for hit rates revealed a significant main effect of Approach/Withdrawal, ($F(1, 48) = 14.58$, $p < .001$, $\eta^2 = .23$), indicating higher hit rates for approach motivated emotions. The main effect of VHF was also significant ($F(1, 48) = 10.82$, $p < .005$, $\eta^2 = .18$), indicating a LVF advantage. Moreover, the interaction between Approach/Withdrawal and VHF was significant ($F(1, 48) = 16.76$, $p < .001$, $\eta^2 = .26$). Simple comparisons revealed a significant LVF advantage for withdrawal motivated emotions, ($t(49) = 6.17$, $p < .001$) but no VHF differences for the approach motivated emotions ($t(49) = .31$, n.s.).

For the response times, a main effect of Approach/Withdrawal was significant, ($F(1, 48) = 31.28$, $p < .001$, $\eta^2 = .40$) with generally faster responses to approach motivated emotions. The main effect of VHF also reached significance ($F(1, 48) = 16.68$, $p < .001$, $\eta^2 = .26$) indicating an advantage in favour of the LVF compared with the RVF. The interaction between Approach/Withdrawal and VHF was not significant ($F(1, 48) = 1.38$, n.s.). Mean hit rates and RTs (M ± SEM) to approach motivated and withdrawal motivated facial expressions for each VHF are presented in Table 3.

Both analyses (hit rates and response times) again did not reveal any significant effects involving Sex (all $F < 2.09$).

		LVF	RVF
Hit rates	Approach	90.83 ± 7.38	90.41 ± 8.30
	Withdraw	90.75 ± 7.01	84.79 ± 8.13
RTs	Approach	857.3 ± 166.4	903.4 ± 185.3
	Withdraw	903.8 ± 173.9	936.2 ± 181.1

Table 3. Mean hit rates and RTs (M ± SD) to approach motivated and withdrawal motivated facial expressions presented in the left visual field (LVF) and right visual field (RVF).

Basic Emotions

For the analysis of basic emotions, hit rates were subjected to a 6 x 2 x 2 ANOVA with repeated measures, with Emotion (anger; disgust; fear; happiness; sadness; surprise) and VHF (LVF/RVF) as within-participants factors and Sex as between-participants factor. A significant main effect of Emotion was revealed (F (1, 48) = 47.67, $p < .001$, $\eta^2 = .50$). There was also a main effect of VHF ($F(1, 48) = 20.18$, $p < .001$, $\eta^2 = .30$). Moreover, the interaction between Emotion and VHF was significant ($F(1, 48) = 21.30$, $p < .001$, $\eta^2 = .31$). Paired t-tests between VHFs revealed a significant LVF advantage for anger, ($t(49) = 2.82$, $p < .01$), fear, ($t(49) = 3.97$, $p < .001$), and sadness, ($t(49) = 9.11$, $p < .001$). Moreover, a RVF advantage was found for happy facial expressions ($t(49) = -3.13$, $p < .005$). Facial expression of surprise only approached significance ($t(49) = 2.60$, $p = .012$) and disgust did not reveal VHF differences ($t(49) = -.88$, $p = .38$). Mean hit rates (M ± SEM) to each specific facial emotion presented in each VHF are displayed in Figure 1.

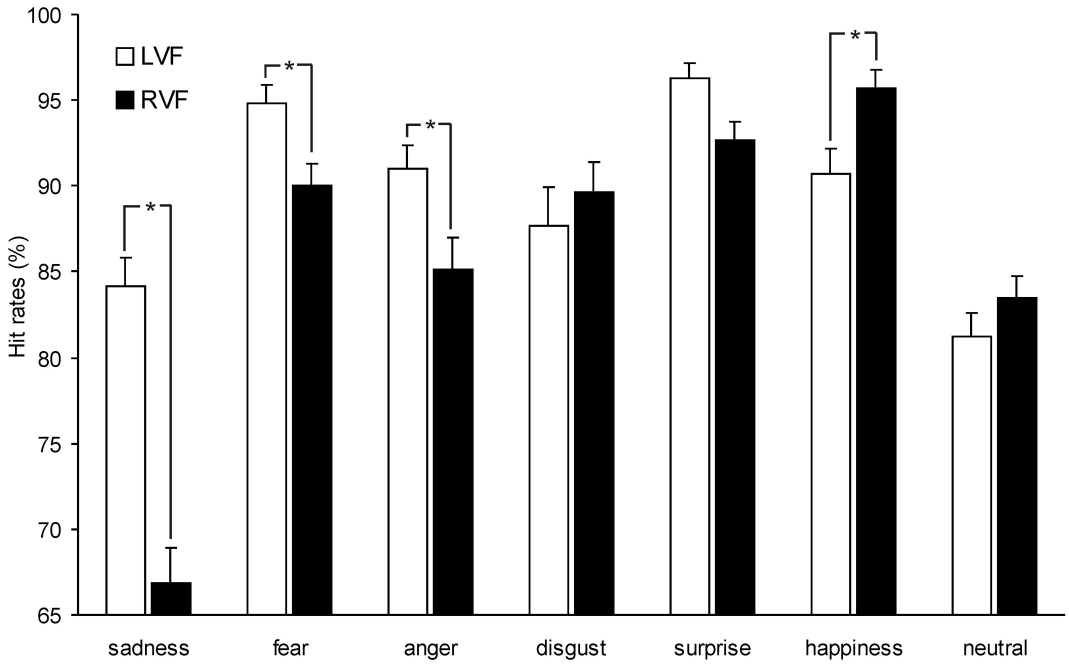

Figure 1. Mean hit rates (M ± SEM) to each specific facial emotion presented in the left visual field (LVF) and right visual field (RVF).

The corresponding analysis for response times also revealed significant main effects of Emotion, ($F(1, 48) = 23.71$, $p < .001$, $\eta^2 = .33$) and VHF ($F(1, 48) = 16.68$, $p < .001$, $\eta^2 = .26$). The significant interaction between Emotion and VHF ($F(1, 48)$

= 3.69, $p < .01$, $\eta^2 = .07$) indicated significant VHF differences in favour of the LVF for anger ($t(49) = -5.31$, $p < .001$), and sadness ($t(49) = -2.71$, $p < .01$). Moreover, a marginally significant LVF and RVF advantage was shown for fear ($t(49) = -2.56$, $p = .013$) and happy ($t(49) = -2.03$, $p = .048$) expressions, respectively. Finally, nonsignificant VHF differences were revealed for disgust ($t(49) = -.35$, n.s.) and surprise ($t(49) = -1.23$, n.s.).

Again, neither the main effect of Sex nor any interaction with Sex were significant (all $F < 2.14$).

Discussion

The aim of the present study was (a) to review VHF studies of hemispheric specialization in facial emotion perception and (b) to reevaluate empirical evidence (including findings of the present study) with respect to the Right Hemisphere Hypothesis, the Valence-Specific Hypothesis and Approach/Withdrawal model of emotion perception. Results from the present analysis testing FCAs of specific facial emotions revealed an LVF/right hemisphere advantage for the perception of angry, fearful, sad, and surprise facial expression in at least one of two dependent variables (hit rates and/or mean RT). Only happy faces revealed an RVF/left hemisphere advantage, at least in hit rates. The present study did not reveal any VHF effects for disgusted and neutral facial expressions. In sum, results of the present study did not account for any of the three models without restrictions. The Right Hemisphere Hypothesis predicts a right hemisphere advantage for all emotional faces. However, face stimuli expressing disgust did not show a VHF effect, neither for hit rates nor mean RT. Happy facial expressions even revealed a left hemisphere advantage, which is clearly in contrast to the prediction by the Right Hemisphere Hypothesis. Although the left hemisphere advantage for happy faces rather supports both versions of the valence hypotheses, the positive facial expression of surprise was found to be right lateralised. Even less support has been found for the Approach/Withdrawal model because the right hemisphere advantage for angry faces (assumed to elicit approach motivation) additionally contradicts with this version of the valence hypothesis.

If VHF effects were averaged across all (or a selection of) specific emotional expressions, a LVF advantage was promoted, supporting the Right Hemisphere

Hypothesis. This is in line with previous VHF studies showing a LVF advantage for facial emotion perception (Alves et al., 2009; Landis et al., 1979; McKeever & Dixon, 1981; Safer, 1981; Suberi & McKeever, 1977; Strauss & Moscovitch, 1981). The majority studies claiming a right hemisphere superiority for facial emotion perception used only a small number of emotions. Also, these studies face the potential limitation that the right hemisphere advantage was driven by face recognition, given that most of these studies did not show an absence of VHF differences for the perception of neutral expressions. This particular caveat can probably be ruled out in the present study because the present study did not find any VHF differences for neutral facial expressions, suggesting that the right hemisphere advantage for emotional perception is relatively independent from face processing.

In favour of the Right Hemisphere Hypothesis, a functional magnetic resonance (fMRI) study using presentation of chimeric faces showed activation in posterior areas of the right hemisphere for processing both happy and sad emotions (Killgore & Yurgelun-Todd, 2007). Additionally, left middle temporal gyrus activation was detected for happy faces adding support to the Valence-Specific hypothesis. The authors suggested that both models are not necessarily in opposition, but may represent different stages of a more complex emotional system. However, the question of a right hemisphere specialization for emotions in general was restricted to only happy and sad emotions. Overall, evidence from neuroimaging studies supporting the Right Hemisphere Hypothesis is rather sparse (Fusar-Poli et al., 2010; Murphy, Nimmo-Smith, & Lawrence, 2003). Also, support for the Right Hemisphere model comes from a lesion study revealing a relationship between impaired emotion recognition after lesions in right inferior parietal and mesial anterior infracalcarine cortices (Adolphs, Damasio, Tranel, & Damasio, 1996). This study did not find impairments in emotion recognition in patients with lesions restricted to the left hemisphere. However, again only happy and sad facial expressions were tested which provides limited support for the RH model. In contrast, studies examining other basic emotions (apart from happiness and sadness) in patients with unilateral lesion seem to support a “negative (only) valence model” (Benuzzi et al., 2004; Burton et al., 2003; Kucharska-Pietura, Phillips, Gernand, & David, 2003; Weniger & Irle, 2002). For example, Weniger and Irle (2002) used a rating task including facial expressions of the six basic emotions and found that right

hemisphere lesion patients rated negative expressions less aroused than left hemisphere lesion patients. A further study revealed that patients with unilateral lesions restricted to the right hemisphere were significantly more impaired in recognizing facial expressions of anger, sadness, fear, disgust, and surprise than patients with left hemisphere lesions (Kucharska-Pietura et al., 2003). Finally, Burton et al. (2003), who investigated recognition of negative facial emotions in unilateral lobectomy patients, found impaired performance in patients who underwent right lobectomy as opposed to patients who underwent left lobectomy.

If none of the models does convincingly predict hemispheric specialization in facial emotion perception, one might speculate that FCAs in facial emotion perception cannot be averaged across specific emotions or valence-specific categories of emotions. This idea has been considered by only a few VHF studies that have examined FCAs for specific emotions (Alves et al., 2009; Asthana & Mandal, 2001; Natale, Gur, & Gur, 1983; Safford & Brandaro, 2010), though only two of them included the six basic emotions (Natale et al., 1983; Safford & Brandaro, 2010). None of these two studies however, have directly compared the three competing models as in the present study. Interestingly, these studies also revealed a LVF advantage for angry faces (Natale et al., 1983; Stafford & Brandaro, 2010) which is consistent with the results of the present study and suggest that anger is processed as a negative emotion compatible with its possible harmful consequences, e.g., aggression (Lazarus, 1991). As in the present study, two of the VHF studies evaluating specific emotions also showed an LVF/right hemisphere advantage for sad faces (Asthana & Mandal, 2001; Natale et al., 1983). Moreover, a superior right hemisphere involvement for the perception of fear is supported by another VHF study (Alves et al., 2009). The LVF advantage reported for the perception of these three negative emotions (anger, fear, and sadness), also consistent with the lesion data cited above (Benuzzi et al., 2004; Burton et al., 2003; Kucharska-Pietura et al., 2003; Weniger & Irle, 2002), suggests that negative emotions are more efficiently perceived through the right hemisphere. Hemispheric specialization for the perception of disgust has been somehow controversial, with one study reporting a LVF (right hemisphere) advantage (Natale et al., 1983), whereas, similar to the present study, Stafford and Brandaro (2010) did not find VHF differences. Although disgust is associated with an unpleasant state and therefore

with negative valence, facial expression of disgust has been also perceived as a funny expression (Fine, 1988; Miller, 1997). This may suggest that the perception of disgust may involve coexisting negative and positive valences that elicit unclear FCA patterns. Concerning the perception of surprise, our results and a previous study (Natale et al., 1983) revealed an LVF/right hemisphere advantage. However, an RVF advantage has also been reported (Stafford & Brandaro, 2010). Surprise involves a startle effect which may trigger a stressful or negative perception. Given that it is also considered to be a positive emotion, however, this may explain the inconsistent laterality findings.

FCAs have also been unclear for the perception of happy faces, with one study (Alves et al., 2009) reporting an LVF/right hemisphere advantage, whereas the results of the present study revealed an RVF/left hemisphere advantage. Alves, Aznar-Casanova and Fukusima, (2009) also found an RVF/left hemisphere superiority for neutral faces. According to the authors, this rather uncommon finding is difficult to explain and might not necessarily indicate a left hemispheric advantage for the perception of neutral expressions but might arise from the specific experimental design. In each trial, the target stimulus (neutral faces) and distractor (emotional faces) were presented simultaneously in the RVF and LVF. If, however, participants applied a response strategy that targeted the easier detectable emotional faces, the apparent RVF advantage for neutral expression might actually reflect a LVF/right hemisphere advantage for emotional face perception in general. In contrast, the present study revealed no VHF differences for the perception of neutral expressions. According with VHF studies examining the perception of specific facial emotions, none of the three proposed models are supported. The data rather suggest a "negative (only) valence model" for facial emotion perception. The lack of support for the Right Hemisphere Hypothesis was mainly based on a consistent LVF/right hemisphere advantage for the perception of anger, fear and sadness but inconsistent for surprise, happiness and disgust. Similarly, data on FCAs between emotions do not follow the valence-specific laterality prediction for happiness, disgust and surprise. Support for the Approach/Withdrawal model is even less convincing given that only FCAs for the perception of fear, and sadness are compatible with the model.

Our data and the literature supporting a "negative (only) valence model", consistently showed an LVF/right hemisphere advantage for a subset of negative

emotions which included anger, fear and sadness. The consistent LVF/right hemisphere advantage for this selection of negative emotions may rely on a common specific attribute of these emotions supporting an "Anger Fear Sad model" (AFS). In fact, marked increases in heart rate were found for anger, fear and sadness which distinguished them from another subset (i.e., enjoyment, surprise) that revealed little change in heart rate, and from disgust, which showed heart rate slowing (Ekman, Levenson, & Friesen, 1983; Levenson, 1992). Although each of these emotions seem to be mediated by specific brain regions, such as the right middle temporal gyrus in fear and sadness (Blair et al, 1999; Morris et al., 1998) and the right orbitofrontal cortex in anger (Blair et al., 1999), their perception may engage an extended right hemisphere neural system (Adolphs et al., 1996). In addition, anger, fear and sadness are particularly associated with the experience of distress, which is linked with heart rate accelerations (Eisenberg & Fabes, 1990). Indeed, the overall performance for response times revealing significantly higher performance in the right hemisphere than the left hemisphere for this particular AFS subset of emotions in the study, support the conjecture that distress-related emotions are more efficiently processed by the right hemisphere. Thus, it might be that an emotional processing system specialised for signalling danger or harmful stimuli (Borod, 1992; Craig, 2005; Fox, 1991) involves right lateralised mechanisms that enable the early allocation of attentional resources to negative stimuli.

Among possible explanations for FCAs it has been argued that brain lateralisation is associated with simple computational advantages allowing adaptive strategies (MacNeilage et al., 2009). For example, FCAs has been associated with advantages such as increase in the speed of predator-evasion responses and increase in neural capacity on the basis of specializing one hemisphere for a particular function (MacNeilage et al., 2009). Given that emotions are closely related to the behaviour of the individual and its environment, these advantages may also apply to the processing of emotions.

In the present study none of the analyses revealed a significant influence of sex (no main effects and interaction). These findings seem to contradict prior reports of sex differences in FCAs (Borod, Koff, White, 1983; Bryden, 1982; Harris, 1978; Killgore & Yurgelun-Todd, 2001; McGlone, 1980;), which also focused on emotional face processing (e.g., Borod et al., 1983; Killgore & Yurgelun-Todd, 2001). A systematic review on VHF studies by Hiscock et al., (1995) reported that

17 out of 92 relevant outcomes show reduced FCAs in females compared to males. An observation that is in line with other reviews and meta-analyses (e.g., Bryden, 1982; Harris, 1978; Hiscock, Perachio, & Inch, 2001; McGlone, 1980; Voyer, 1996, 2011). However, the effect sizes for sex differences in FCAs seem to be rather small, accounting for only about 1% of the variance in laterality measures (Hiscock, Israelian, Inch, Jacek, & Hiscock-Kalil, 1995) or even less (e.g., Voyer, 1996, 2011). Inconsistencies in the literature on sex differences in FCAs may occur for various reasons. One critical issue is the lack of control of the sex hormonal environment. For example, it has been shown that sex differences in FCAs partly depend on the cycle phase in which female participants were tested (e.g., Hausmann & Güntürkün, 2000; Hausmann, Becker, Gather, Güntürkün, 2002; Weis, Hausmann, Stoffers, Sturm, 2011; Weis, et al., 2008; for review see: Hausmann & Bayer, 2010). Specifically, the majority of these studies suggest that sex differences in hemispheric asymmetries do not exist (or are at least significantly reduced) when women were tested during the menstrual phase. Whether FCAs in emotional facial perception is affected by sex hormones remains still speculative. However, it should be noted that that FCAs in a face-matching task have previously been shown to fluctuate across the menstrual cycle (Hausmann & Güntürkün, 2000). Moreover, there is some evidence that emotional face perception in general is affected by sex hormones (Pearson and Lewis, 2005; Conway et al., 2007; Derntl et al., 2008). For example, higher accuracy for detecting fearful faces was found during late preovulatory phase, when estrogen levels are high, than during menstruation when estrogen levels are low (Pearson and Lewis, 2005).

In sum, the current findings revealed that FCAs for the perception of specific rather than averaged facial emotions do not support the Right Hemisphere Hypothesis, Valence-Specific Hypothesis or the Approach/Withdrawal model. In contrast, this study as well as other VHF studies (Alves et al., 2009; Asthana & Mandal, 2001; Natale et al., 1983; Safford & Brandaro, 2010) and studies on patients with unilateral lesion (Benuzzi et al., 2004; Burton et al., 2003; Kucharska-Pietura et al., 2003; Weniger & Irle, 2002) show that not all basic emotions are equally functionally organised in the brain and only those emotions clearly negative in valence indicate a consistent LVF/right hemisphere advantage.

Postscript to Chapter 2

The present chapter investigated the functional brain organisation of emotion perception in the healthy brain. Such emotional organisation of the brain may be influenced by valence and, or motivational attributes. Thus, to take into account the potential influence from these aspects of emotion the present study tested basic asymmetry models in emotion perception. Although results did not thoroughly fit any of the models' predictions, laterality seemed more robust for negative than for any other emotion. As the present thesis involves studies in a related hypomanic trait (Chapter 3) and BD euthymia (Chapters 4 to 6), a key state for linking acute and usual mood, an implicit general goal of this thesis is to assess laterality across a bipolarity continuum. From this perspective, the present study assessing lateralisation in healthy controls provides with the basis for studying deviations in the brain organisation of BD related conditions. Also to follow on the general goal of studying a BD continuum, euthymic BD patients were also tested with the exact same emotional face task as in the present study. However, poor performance of BD patients suggested that the task is too difficult for patients and discouraged us from including these data in the thesis.

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Chapter 3

The previous chapter presented a study assessing laterality of emotion perception in healthy controls. Robust FCA patterns were only found for negative expressions. A possible explanation for these findings is that emotion perception may not directly reflect the organisation of the brain in emotional processing. An alternative path for understanding the functional brain organisation of emotional processing is to study the experience of emotion. A prototypal phenomenal "feel" is found in the acute mood states of BD. Manic or depressive mood in BD are known to influence atypical FCAs (e.g., Allen, Iacono, Depue, & Arbisi, 1993; Altshuler et al., 2008; Foland et al., 2008; Harmon-Jones et al. 2002, 2008; Jogia, Haldane, Cobb, Kumari, & Frangou, 2008; Kano, Nakamura, Matsuoka, Iida, & Nakajima, 1992; Liu et al., 2012; Nusslock et al., 2012; Strakowski et al., 2011). It is possible that these atypical FCA patterns reflect strong influence of an experiential component in the processing of emotions. In fact, previous models have hypothesised that in the face of incoming emotional stimulation, emotional responses act as an organising force, 'hijacking' the entire system and interrupting other on going processes (Oatley & Johnson-Laird, 1987). If in fact the experience of emotion has such an influential role in emotional processing, one would expect to find differences in functional brain organisation in BD related conditions that are symptom free. Thus, euthymic BD patients should involve similar deviations in FCAs. However, this would only imply similar effects at non-symptomatic clinical levels. In order to extend these effects to the healthy brain, the influence of emotional experience should be also observed in, for example, individuals with personality traits associated with mood symptoms that are not affected by clinical diagnosis.

In sum, an experiential component of the functional brain organisation in emotional processing may be reflected in that healthy people with affective traits process emotions differently. To address this question, the present study examines FCAs in individual with hypomanic related traits associated with mood swings (Gruzelier, 1996) and with hypomanic symptoms (Kwapil et al., 2000).

Atypical lateralisation in emotional prosody in men with schizotypy

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Abstract

Individuals high in schizotypy have been shown to reveal reduced lateralisation in verbal processing which may be influenced by an impaired left hemisphere performance. However, little is known about schizotypy and right hemisphere functions such as emotional perception. The present study focuses on atypical lateralisation in language and emotional prosody in Impulsive Non-conformity (IMP), a specific aspect of schizotypy. Forty-one participants (20 females) performed a dichotic listening linguistic and emotional prosody task, which typically shows a right ear advantage (REA) and left ear advantage (LEA), respectively. A median split based on the IMP scale included in the Oxford-Liverpool Inventory of Feelings and Experiences was used to divide the sample into high and low scorers. The results revealed a selective reduction of the LEA in the prosody task in high-IMP males. Females high and low in IMP revealed typical lateralisation in both tasks. The results indicate that high-IMP males are especially prone to atypical lateralisation in emotional prosody which parallels those findings in male patients with schizophrenia. The results suggest similarities in sex-specific atypical brain organisation between schizotypy and schizophrenia.

Laterality, 17, 533-548.

Introduction

Atypical lateralisation in language in schizophrenia is well documented by behavioural studies using the dichotic listening (DL) paradigm (e.g., Bruder et al., 1999; Grosh, Docherty, & Wexler, 1995; Loberg, Hugdahl, & Green, 1999). The DL paradigm is a non-invasive technique for the examination of temporal lobe functions, and language lateralisation in particular. This technique involves the presentation of stimuli simultaneously to the right and left ear. Lateralization in language is normally reflected by a better reproduction of verbal stimuli presented to the right ear, corresponding to the left hemisphere, a phenomenon called right ear advantage (REA) (Hugdahl, 1988). The first functional neuroimaging study with a dichotic listening paradigm found that an REA, using consonant-vowels dichotically presented, resulted in greater left temporal lobe activation as detected by oxygen positron emission tomography (Hugdahl et al., 1999). More recently the REA has repeatedly shown to correlate with left-lateralised brain activation as determined by functional magnetic resonance imaging (fMRI) (Fernandes, Smith, Logan, Crawley, & McAndrews, 2006; van Ettinger-Veenstra et al., 2010). In line with fMRI studies in patients with schizophrenia (e.g., Li et al., 2007; Woodruff et al., 1997), a reduced REA has also been revealed by DL studies using fused-words (e.g., Bruder et al., 1999) and consonant-vowels as stimuli (e.g., Grosh et al., 1995). Considering a dominance of the left hemisphere as the key element of language organisation, schizophrenia might be understood as a failure or delay in the process of acquiring dominance for fundamental aspects of language (Crow, 1997). Alternative theories of atypical functional cerebral asymmetries in schizophrenia have argued for a left hemisphere overactivation (Flor-Henry, 1976; Venables, 1977) or impairment in the ability to transfer information between the two hemispheres (Green, Glass & O'Callaghan, 1979; Rosenthal & Bigelow, 1972).

An independent flow of research has also linked schizophrenia with deficits in emotional prosody, a specific component of emotion perception, frequently assessed by sentences spoken in emotional and neutral intonation of voice (e.g., Bach, Buxtorf, Grandjean, & Strik, 2009; Kucharska-Pietura, David, Masiak, & Phillips, 2005; Mitchell, Elliott, Barry, Cruttenden, & Woodruff, 2004). Moreover, an fMRI study by Mitchell et al. (2004) identified that the typical right > left temporal lobe

activation for emotional prosody was reversed in patients with schizophrenia, suggesting a right hemisphere trait deficit for schizophrenia.

Given that psychotic-like symptoms are also present in normal individuals as schizotypic personality traits, atypical functional cerebral asymmetries (FCAs) may also affect a portion of the population at the higher end of the healthy schizotypy spectrum. In fact, as in schizophrenia, laterality research in schizotypy has shown atypical lateralisation in language (e.g., Kravetz, Faust, & Edelman, 1998; Leonhard & Brugger, 1998; Pizzagalli, Lehmann, & Brugger, 2001). However, interpretation of these findings is inconsistent, with some studies suggesting impaired left hemisphere semantic processing (e.g., Kravetz et al. 1998; Raine & Manders, 1988) and others proposing right hemisphere overactivation (e.g., Leonhard & Brugger, 1998; Pizzagalli, et al. 2001). Additional inconsistencies come from psychophysiological studies reporting left hemisphere overactivation in schizotypy (Kidd & Powell, 1993; Raine, Venables, Mednick, & Mellingen, 2002).

It should be noted, however, that FCAs in schizotypy have rarely been investigated for right-hemisphere functioning and emotion perception in particular. One of the few studies compared men high and low in schizotypy on a lateralised version of the emotional stroop paradigm (van Strien & van Kampen, 2009). The task requires identifying the ink colour of emotional and neutral words, presented to the left and right visual half-fields, whilst ignoring their semantic content. Participants high in schizotypy exhibited more affective interference for colour naming when presented with negative emotional words to the left visual half-field than participants low in schizotypy.

This finding indicates a reduced right hemisphere advantage in colour naming (van Strien & van Kampen, 2009). Lateralization and particularly right hemisphere functioning in schizotypy were also examined by a study where participants were asked to make emotional decisions to chimeric faces and emotional faces (visual-half field paradigm) (Mason & Claridge, 1999). The expected left visual field advantage, corresponding to the right hemisphere, was reduced for both tasks in male participants high in Unusual Experiences, one of the factors of schizotypy, but not in females (Mason & Claridge, 1999). As these studies used either dichotic listening or visual half field methods, it is difficult to determine whether decreased lateralisation reflects impaired left hemisphere or right hemisphere functioning. Nonetheless, these studies revealed a relationship between atypical lateralisation and schizotypy which

may involve right hemisphere functioning. Also, these findings suggest that schizotypy males might be particularly prone to this effect.

Additionally, atypical lateralisation has been linked to an active schizotypy syndrome (i.e., behavioural over-activity) and to a withdrawn schizotypy syndrome (i.e., reduced behavioural activity) (Gruzelier & Richardson, 1994). This study assessed lateralisation with the recognition memory test (Warrington, 1984) by comparing recognition memory for words with memory for unfamiliar faces. The active schizotypy syndrome, identified with the Impulsive Non-conformity (IMP) scale included in the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE), showed a word > face superiority, attributed to a left hemisphere advantage. On the contrary, the withdrawn schizotypy syndrome, measured with the Introvertive Anhedonia scale from the O-LIFE, exhibited a face > word superiority, interpreted as a right hemisphere advantage (Gruzelier & Richardson, 1994). Thus, the active and withdrawn schizotypy syndromes were linked to different cognitive patterns which have been interpreted by the authors as an indicator of opposite laterality patterns. However, given that the test used by that study is a highly indirect measure for lateralisation (Hermann, Connell, Barr, & Wyler, 1995), the conclusions drawn by the authors remains speculative and warrants further examination with a more direct measure for lateralisation.

Among all the schizotypy traits, IMP is particularly intriguing given its relationship with Psychoticism (Gruzelier, 1996; Gruzelier & Richardson, 1994), and consequently with psychosis proneness (Allen, Chapman, Chapman, Vuchetich, & Frost, 1987; Chapman et al., 1984). IMP represents a valuable model for identifying elements in the psychopathophysiology of schizophrenia within the healthy population (Gruzelier, 1996; Gruzelier & Richardson, 1994). There are a number of studies investigating IMP and cognitive functions in non-clinical participants (e.g., Gruzelier & Richardson, 1994; Kravetz et al., 1998). However, only one study directly measured lateralisation in linguistic processing in IMP (Kravetz et al., 1998). Additionally, one study drew indirect conclusions about lateralisation (i.e., Gruzelier & Richardson, 1994), but as stated above the results are methodologically limited. More recently, Chapman et al., (2011), investigated handedness and its relationship with different dimensions of schizotypy. They found a weaker hand preference, as indicated by the absolute laterality index from the Annett Handedness Inventory (Annett, 1970), in individuals with higher scores on the

Hypomania/Impulsivity Non-conformity scale and the Perceptual Aberration/Magical Ideation scale from the Psychosis Proneness Questionnaire (Hay et al., 2001). Given that mixed handedness represents a developmental disturbance in the establishment of normal lateralisation for manual dominance (Reilly et al., 2001), these findings also suggest a link between atypical lateralisation and IMP.

The present study therefore focuses on IMP and its putative association with atypical lateralisation in both linguistic and emotional prosody. Hence, a DL paradigm that includes a linguistic and emotional prosody task has been applied. This paradigm has frequently shown to produce a REA in the linguistic task and a LEA in the prosodic task, corresponding to the left and right hemisphere, respectively (Grimshaw, Kwasny, Covell, & Johnson, 2003). We predict atypical lateralisation in emotional and linguistic information processing, particularly in individuals high in IMP.

Sex differences in dichotic listening (see Hiscock, Inch, Jacek, Hiscock-Kalil, & Kalil, 1994, for a review and meta-analysis) as well as sex differences in schizotypy (Fonseca-Pedrero, Lemos-Giraldez, Muniz, Garcia-Cueto, & Campillo-Alvarez, 2008) have been reported previously. Given that there is some evidence that atypical FCAs in schizotypy are sex-specific (e.g., Broks, 1984; Gruzelier & Richardson, 1994; Mason & Claridge, 1999) we also included sex in our statistical design. As already mentioned above, these studies found that schizotypy males but not females exhibit atypical FCAs (e.g., Broks, 1984; Gruzelier & Richardson, 1994; Mason & Claridge, 1999). Therefore, we predict atypical lateralisation in emotional and linguistic information processing to be particularly pronounced in male individuals high in IMP.

Methods

Participants

The original sample consisted of 64 healthy students from the Department of Psychology (N = 40) and other faculties at Durham University (N = 14). Students from the Department of Psychology were recruited from the participant pool, which consists of a large body of undergraduate students registered on psychology modules. These students earn course credit by participating in psychology research. Students from other faculties were recruited via an advertisement on the university

intranet and received a payment for their participation. In line with the intention to investigate FCAs in a homogeneous group, 13 participants who were either ambidextrous or who showed no pronounced handedness as assessed with the Edinburgh Inventory (Oldfield, 1971), were excluded from the analyses. Thus, a final total of 41 individuals (20 females) remained in the analysis sample. The mean age of women was 21.55 years (SD = 3.87; range: 18–33 years) and 22.38 years (SD = 5.10; range: 18–39 years) for men. All participants were right-handed as determined with the Edinburgh Inventory (Oldfield, 1971). The asymmetry-index (LQ) provided by this test is calculated as $[(R-L)/(R + L)]\times100$, resulting in values between −100 and +100, and describes a continuum from extreme sinistrality to extreme dextrality. The mean LQ of women was 78.97 (SD = 20.20; range: 40–100) and 84.60 (SD = 17.51; range: 50–100) for men. All participants reported to have no hearing deficits or previous psychiatric history and were native English speakers.

Procedure and Materials

Personality questionnaire

To identify Impulsive Non-conformity (IMP), the short version of the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE; Mason, Linney, & Claridge, 2005) was used. The O-LIFE short scales include four factors: (i) Unusual Experiences, (ii) Cognitive Disorganisation, (iii) Introvertive Anhedonia, and (iv) IMP. The IMP scale, which is in the focus of the present study, is akin to Eysenck's Psychoticism scale (Eysenck & Eysenck, 1975) and measures impulsive and anti-social aspects of schizotypy. It is identified by items such as 'Would you like other people to be afraid of you?' and 'Do you at times have an urge to do something harmful or shocking?'. The O-LIFE short scales comprise Yes/No responses. The score is calculated as the sum of all positive answers.

Dichotic Listening Tasks

The DL task consisted of a linguistic (word identification) and a prosodic task. The linguistic DL task requires participants to recognize a particular word target and typically generates a REA corresponding to the left hemisphere. The prosodic DL task requires participants to recognize a particular emotional tone of voice target

which generates a LEA corresponding to the right hemisphere. The stimulus set for both tasks consists of four two-syllable words: “bower”, “dower”, “power”, and “tower”, spoken in angry, happy, neutral, and sad tones of voice (Bryden & MacRae, 1989; and in experiment 1 of Grimshaw et al., 2003). The words were spoken in New Zealand English by a male voice (Grimshaw, Séguin, & Godfrey, 2009). The stimuli consist of all possible pairings of words and emotions with the constraint that a different word and a different tone of voice are presented to each ear on each trial, yielding a total of 72 stimulus pairs. Both tasks consisted of four blocks of 72 trials, for a total of 288 trials (excluding 16 practice trials). Word target and voice target as well as block order were counterbalanced across participants. Orientation of supraaural headphones with circumaural cushions was reversed across participants. Participants were instructed to listen either to a word target or voice target, providing a single response on each trial. In line with Grimshaw et al (2003), they were not informed about the dichotic nature of the stimuli. Participants monitored for a specified target word (linguistic task) for two blocks of trials, and for a specified target tone of voice (prosodic task) for two blocks of trials. They indicated their response by button press as quickly and accurately as possible using the index (for present) or middle finger (for absent). Each word or tone of voice was present in 50% of the trials, 25% in the left ear and 25% in the right ear. The experiment was controlled by E-Prime (Psychology Tools Inc., Pittsburgh, PA) on a desktop PC. Response times (RT) and accuracy were recorded as dependent measures. As processing for happy, angry, and sad prosodies in this prosody task shown to equally involve right hemisphere lateralisation (Bryden & MacRae, 1989; Grimshaw et al., 2009), in line with a general right hemisphere specialization for prosody (Borod et al., 1998; Buchanan et al., 2000; Erhan, Borod, Tenke, & Bruder, 1998) data will not be analysed in terms of valence. To investigate the relationship between impulsive non-conformity as a continuous measure and the degree of lateralisation, an asymmetry-index (AI) was calculated as (D – SD) / (D + SD), with D and SD referring to the dominant hemisphere and subdominant hemisphere, respectively.

Results

Personality questionnaire

The O-LIFE was scored for each schizotypy scale: Unusual Experiences (range: 0-12), Cognitive Disorganisation (range: 0-11), Introvertive Anhedonia (range: 0-10), and IMP (range: 0-10). Independent *t*-tests were conducted to compare males and females on the scoring for each scale (Mean ± standard deviation): Unusual Experiences (males: 3.14 ± 2.45, females: 3.75 ± 3.09), Cognitive Disorganisation (males: 6.00 ± 2.62, females: 5.15 ± 3.04), Introvertive Anhedonia (males: 2.57 ± 2.18, females: 1.45 ± 1.60), IMP (males: 3.52 ± 1.77, females: 3.65 ± 2.83). None of *t*-tests revealed significant sex differences (all $t(39) < 1.86$, n.s.).

Given that IMP taps into psychosis proneness (Gruzelier, 1996; Gruzelier and Richardson, 1994) and has been associated with Psychoticism (Allen et al., 1987; Chapman et al., 1984) the following analyses will focus on IMP. However, the other scales will also be considered. We performed a median split based on IMP (low scores: 0-3; high scores: 4-10). The sample was divided into four subgroups: high-IMP males (Mean ± SD; 5.22 ± 1.00, N = 9), low-IMP males (2.25 ± 0.80, N = 12), high-IMP females (6.20 ± 1.30, N = 10) and low-IMP females (1.10 ± 0.80, N = 10).

Dichotic listening test

IMP O-LIFE

Accuracy

Hit rates were subjected to a mixed analysis of variance (ANOVA), with Task (linguistic/prosodic) and Ear (left/right) as within-subject factors, and Sex and IMP (high/low) as between-subject factors. The ANOVA revealed a significant Ear by Task interaction, $F(1, 37) = 54.17$, $p < .001$, $\eta^2 = .59$, indicating the expected REA and LEA for the linguistic and prosodic task, respectively. The 3-way interaction between Task, Ear, and Sex was also significant, $F(1, 37) = 7.24$, $p < .05$, $\eta^2 = .16$. Moreover, there was a significant Ear by Task by Sex by IMP interaction $F(1, 37) = 6.54$, $p <. 05$, $\eta^2 = .15$. No other effect approached significance, all $F < 3.07$. Mean hit rates are shown in Figure 1 and Table 1.

Task	Sex	IMP	LE	RE	N
Linguistic	Males	High	71.30 ± 6.92	80.56 ± 5.01	9
		Low	59.26 ± 5.99	79.63 ± 4.34	12
	Females	High	68.61± 6.57	87.78 ± 4.75	10
		Low	64.44 ± 6.57	79.44 ± 4.70	10
Prosody	Males	High	70.99 ± 6.12	79.01 ± 5.90	9
		Low	76.85 ± 5.30	66.2 ± 5.11	12
	Females	High	75.56 ± 5.81	57.22 ± 5.59	10
		Low	79.72 ± 5.81	62.78 ± 5.60	10

Table 1. Percent of hit rates (M ± S.E.M.) to stimuli presented to the left ear (LE) and to the right ear (RE) for male and female participants high and low in Impulsive Non-conformity (IMP). The results for the linguistic DL task are shown at the top and those for the prosodic DL task are shown at the bottom.

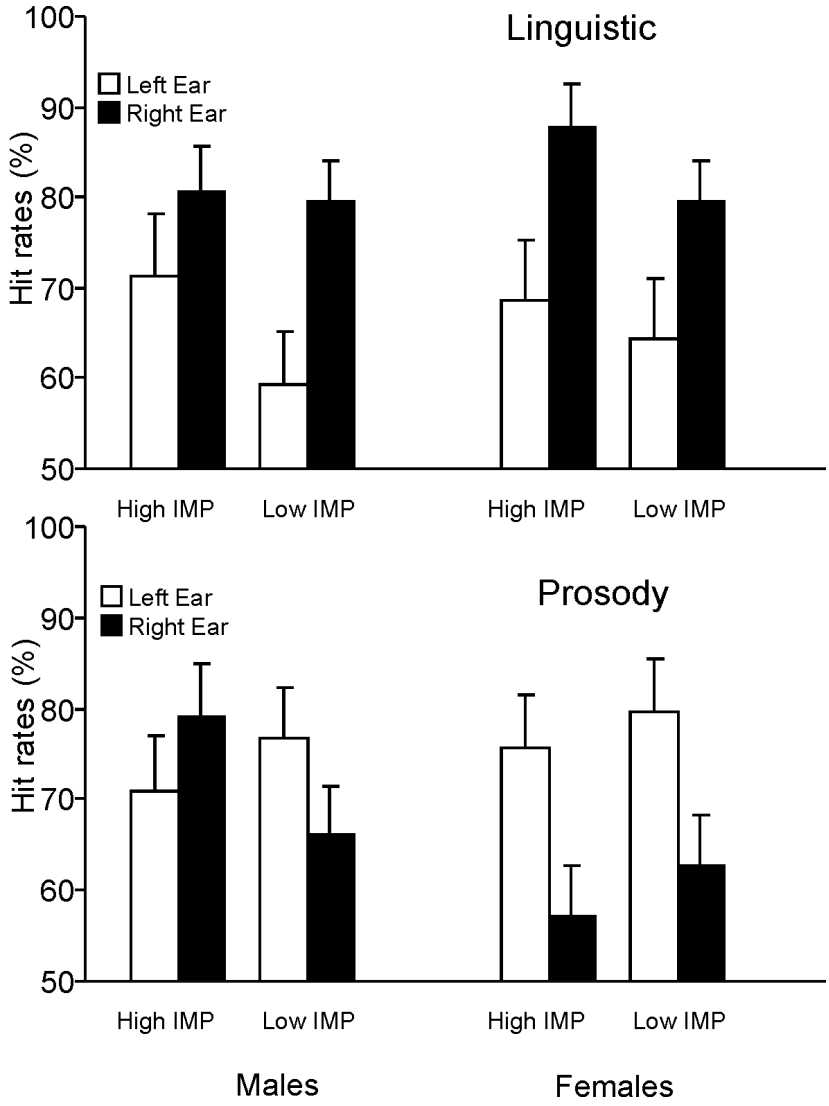

Figure 1. Correct responses (%) and standard errors to stimuli presented to the left ear (white bars) and to the right ear (black bars) for male and female participants high and low in Impulsive Non-conformity (IMP). The results for the linguistic DL task are shown at the top and those for the prosodic DL task are shown at the bottom.

To examine the nature of the 4-way interaction, hit rates were further analysed in two separate ANOVAs, one for each task. Hit rates for the linguistic task were subjected to a mixed ANOVA, with Ear (left/right) as within-subject factor, and Sex and IMP (high/low) as between-subject factors. The analysis yielded a significant REA, $F(1, 37) = 21.79$, $p < .001$, $\eta^2 = .37$. No other effect approached significance (all $F < 1.95$, n.s.).

The corresponding analysis for the prosodic task revealed a significant LEA ($F(1, 37) = 18.46$, $p < .001$, $\eta^2 = .33$). The interaction between Ear and Sex was also significant ($F(1, 37) = 13.70$, $p < .001$, $\eta^2 = .27$). Moreover, there was a significant Ear by Sex by IMP interaction, $F(1, 37) = 5.17$, $p < .05$, $\eta^2 = .12$. Post hoc paired *t*-tests (Bonferroni) revealed a significant LEA in low-IMP males ($t(11) = 4.45$, $p < .001$), but not in high-IMP males ($t(8) = -1.52$). In contrast, low-IMP females ($t(9) = 3.77$, $p < .005$) and high-IMP females ($t(9) = 3.32$, $p < .01$) revealed significant LEAs.

Response times

The corresponding analyses for median RTs revealed a significant main effect of Task, ($F(1, 37) = 35.62$, $p < .001$, $\eta^2 = .49$), with faster responses for the linguistic task, than for the prosodic task. The interaction between Sex and IMP was also significant, ($F(1, 37) = 4.65$, $p < .05$, $\eta^2 = .11$). There was also a significant interaction between Ear and Task, $F(1, 37) = 28.87$, $p < .001$, $\eta^2 = .43$, and this effect significantly interacted with Sex, ($F(1, 37) = 4.43$, $p < .05$, $\eta^2 = .10$). Moreover, the interaction between Ear, Task, Sex, and IMP was significant ($F(1, 37) = 5.54$, $p < .05$, $\eta^2 = .13$). No other effect approached significance (all $F < 1.89$, n.s.). Mean response times are shown in Table 2.

Task	Sex	IMP	LE	RE	N
Linguistic	Males	High	901 ± 64.04	835 ± 47.77	9
		Low	936 ± 55.46	872 ± 41.37	12
	Females	High	1039 ± 60.76	880 ± 45.31	10
		Low	811 ± 60.76	774 ± 45.31	10
Prosody	Males	High	1052 ± 78.78	1023 ± 79.28	9
		Low	1126 ± 68.23	1190 ± 68.66	12
	Females	High	1044 ± 74.74	1149 ± 75.21	10
		Low	926 ± 74.74	1005 ± 75.21	10

Table 2. Response time in ms ± S.E.M. to stimuli presented to the left ear (LE) and to the right ear (RE) for male and female participants high and low in Impulsive Non-conformity (IMP). The results for the linguistic DL task are shown at the top and those for the prosodic DL task are shown at the bottom.

Similarly to accuracies, median RTs were further subjected to mixed ANOVA, with Ear (left/right) as within-subject factors, and Sex and IMP (high/low) as between-subject factors, separately for each DL task. In line with the analysis of hit rates, the ANOVA for the linguistic task revealed a significant REA, $F(1, 37) = 14.86$, $p < .001$, $\eta^2 = .28$. There was also a Sex by IMP interaction, ($F(1, 37) = 4.32$, $p < .05$, $\eta^2 = .10$). No other effect was significant, (all $F < 2.14$, n.s.).

In the corresponding analysis for the prosodic task, only the main effect of Ear approached significance, $F(1, 37) = 6.18$, $p < .05$, $\eta^2 = .14$, indicating the expected LEA. No other effect approached significance (all $F < 3.13$, n.s.).

Other O-LIFE scales

When the participants were grouped based on the other O-LIFE scales (Unusual Experiences, Cognitive Disorganisation, Introvertive Anhedonia), and analysed using the same ANOVA design as mentioned previously, none of the ANOVA revealed significant main effects or any interactions with the grouping variable in accuracy (all $F < 2.81$, n.s.). For response time, the only significant effect was found for Cognitive Disorganisation. Here, the interaction between the grouping variable, Task and Ear was significant ($F(1, 37) = 5.27$, $p < .05$, $\eta^2 = .12$). For the prosodic task, alpha adjusted posthoc *t*-tests revealed a reduced LEA for participants low in Cognitive Disorganisation ($t(15) = -2.8$, $p < .05$) but not for participants high in Cognitive Disorganisation ($t(24) = -1.35$, n.s.).

Correlation analyses between AI and IMP scores

To further explore the relationship between IMP as a continuous measure and the degree of asymmetry (based on hit rates and response times), bivariate correlations between AI and IMP scores were calculated for each task and each sex separately. The results revealed a significant negative correlation between IMP and AI for hit rates in prosody in men, indicating that high IMP scores were related to reduced lateralisation in men ($r(21) = -.61$, $p = .004$), a finding that corresponds to the ANOVA result. No other correlation approached significance, neither for hit rates nor for response times, all $r < \pm .32$, n.s.

Discussion

The results of the present study show that atypical lateralisation in emotional prosody can be linked to IMP. The LEA for emotional prosody was selectively reduced in high-IMP males. Female participants showed pronounced LEA independently of high or low IMP. Correspondingly, IMP scores were negatively related with the degree in asymmetry for the prosody task (hit rates) in men, supporting a sex-specific association between schizotypy and reduced lateralisation. In the linguistic task, all groups revealed pronounced REAs. The results suggest that high-IMP males are especially prone to atypical lateralisation in emotional prosody.

In contrast to the present study, previous research has shown that schizotypy can be linked to atypical language lateralisation (e.g., Kravetz et al., 1998; Pizzagalli et al., 2001). This controversy might arise from different aspects of schizotypy. For example, magical ideation as one specific aspect of schizotypy, which has been linked to disordered thoughts, revealed associations with atypical lateralisation in language (Leonhard & Brugger, 1998; Pizzagalli et al., 2001). IMP, however, has been associated with mood swings (Gruzelier, 1996) and with hypomanic symptoms (Kwapil et al., 2000). This might explain why the present study is more likely to detect atypical lateralisation in emotional prosody than in the linguistic task. There is only one study that reported atypical lateralisation in language processing in high-IMP males (Kravetz et al., 1998). Similar to the present study, however, it was the right hemisphere which was particularly affected.

The present results also revealed a reduced LEA for emotional prosody in participants with low but not high scores in cognitive disorganisation, suggesting a right hemisphere involvement. Compatible with this finding, a study investigating the modulatory effect from schizotypy in FCAs, have claimed a right hemisphere shift of function (Herzing, Tracy, Munafo, & Mohr, 2010). This conclusion was grounded on findings of an association between increasing cognitive disorganisation and greater right hemisphere reliance, reflected by a lateralised facial decision task. In this task participants were required to identify the gender of sexually-dimorphic composite faces. The right hemisphere shift in cognitive disorganisation was also based on the finding of a reduced left hemisphere asymmetry in a lexical decision task. Another study found poorer left hemisphere performance in participants with high cognitive disorganisation using a VHF lexical decision task (Kravetz et al.,

1998). Thus regardless of function, cognitive disorganisation may involve overreliance on the right hemisphere as shown in facial (Herzing et al., 2010), language (Herzing et al., 2010; Kravetz et al., 1998), and emotional processing (present study). In the present findings this was reflected on a right hemispheric tendency in emotional prosody associated with cognitive disorganisation. According with a right hemisphere shift of function, cognitive disorganisation should also relate to pronounced right hemisphere involvement in left hemisphere dominant tasks, such as the DL linguistic task of the present study. However, the typical REA (corresponding with the left hemisphere) in the linguistic task was not affected by cognitive disorganisation. This raises the question of why cognitive disorganisation only related to right hemisphere lateralisation in the emotional prosody. From a continuum perspective, cognitive disorganisation may underlie functional brain organisation ranging from adaptive to more dysfunctional effects. In the present study cognitive disorganisation scores may have lied at the adaptive end of the continuum and therefore only related to enhanced but not dysfunctional performance selectively reflected in the prosody task.

Atypical lateralisation in schizotypy males, but not in females has also been shown in a previous study using a dichotic story task (Broks, 1984) and in a verbal visual half-field study (Broks, Claridge, Matheson, & Hargreaves, 1984). Similarly, atypically reduced lateralisation in the present study was present in high-IMP males but not in females. Our results are also in line with Gruzelier and Richardson (1994) showing indirect support for atypical lateralisation in high-IMP males based upon memory recognition for words and unfamiliar faces. In this study males with a word > face superiority had higher IMP scores than males with face > word superiority, which was interpreted by the authors as atypical lateralisation suggesting reduced right hemisphere advantage.

Given that the emotional prosody DL task used here has been shown to rely particularly on the activity of the right superior temporal gyrus (Buchanan et al., 2000), the main finding of the present study of a reduced right hemisphere advantage for emotional prosody in high-IMP males suggests an altered right temporal function. In fact, reduced activity of the right temporal lobe was detected in schizotypy by electroencephalography (Mientus et al., 2002). Likewise, findings from an fMRI study in schizophrenia point to increased left-lateralised activation in the temporal cortex during emotional prosody (Mitchell et al., 2004) suggesting that

the left hemisphere may compensate for functions (i.e., emotional prosody) normally subserved by the right hemisphere. Therefore, the present findings of reduced LEA for emotional prosody in high-IMP males suggests that the right temporal area might be a brain substrate for schizotypy, similarly to schizophrenia. It is important to consider, however, the inconsistencies in the literature on lateralisation and schizophrenia (e.g., Bartley, Jones, Torrey, Zigun, & Weinberger, 1993; Gur, 1978; Gur et al., 1985; Kulynych, Vladar, Fantie, Jones, & Weinberger, 1995; Kulynych, Vladar, Jones, & Weinberger, 1996). While some authors argue for a left hemisphere (e.g., Gur, 1978; Gur et al., 1985), or right hemisphere dysfunction (e.g., Cutting, 1994; David, 1994; Mitchell et al., 2004), others have even failed to report abnormal laterality in schizophrenia, challenging the hypothesis of atypical asymmetries in this condition (Bartley et al., 1993; Deep-Soboslay, et al., 2010; Kulynych et al., 1995, 1996). Given that most of these studies vary in their methodological approaches to assess structural and functional asymmetries, inconsistencies across studies may be explained in terms of sensitivity of the methods to reliably detect atypical asymmetries in schizophrenia.

The sex-effect selectively shown in the high IMP group is consistent with previous studies using a consonant-vowel syllables DL task which repeatedly revealed no sex differences in non-clinical subjects (e.g., Hugdahl, Carlsson, & Eichele, 2001). Moreover, the sex-specific dissociation in atypical lateralisation in IMP (Gruzelier & Richardson, 1994; present study) and in schizotypy (e.g., Broks, 1984; Gruzelier & Doig, 1996) might also be related to emotional functioning as reported in schizophrenia. Specifically, sex differences in lateralisation in emotional prosody in IMP identified by the present study can be also found in schizophrenia (Bozikas et al., 2006; Scholten, Aleman, & Kahn, 2008).

For example, using audio-recorded sentences in emotional and neutral tones of voice, Bozikas et al. (2006) reported impairments in the identification of emotional prosody in male patients with schizophrenia compared to male controls but there were no differences among female groups. However, it should be noted that patients with schizophrenia of this study were on antipsychotics. Thus, confounding pharmacological effects cannot be ruled out. A study that did control for medication, found a relative female advantage for recognizing emotional tones to be preserved in patients with schizophrenia (Scholten et al., 2008).

The mean age of our sample was relatively young (22.38 ± 5.01 years) which might challenge schizotypy as a potential model to understand functional brain organisation in schizophrenia. Although inconsistencies in the age distribution exist (Schürhoff et al., 2004), Panariello et al. (2010) reported an early-onset subgroup with a cut-off point at 22 years. Interestingly, 78.9% of the early onset subgroup were male, suggesting that (a) men are more likely to develop schizophrenic symptoms at a younger age, and (b) the age distribution in the present study is particularly comparable to early onset patients with schizophrenia.

The sex differences reported in the present study are in line with evidence showing higher IMP scores in males than in females (Fonseca-Pedrero et al., 2008). Thus, alterations of lateralisation in emotional prosody (present study) and emotional dysfunctioning seem to be more evident in males than females (Bozikas et al., 2006; Scholten et al., 2008), perhaps as a result of different sex hormonal environments. In fact, the course of illness in schizophrenia seems to be influenced by periods of sex hormonal changes (Kendell, Chalmers, & Platz, 1987). Estrogens possess neuroprotective properties which appear to protect against neuronal atrophy in schizophrenia (Rao & Kölsch, 2003). There is also evidence showing that estrogens influence FCAs (see Hausmann & Bayer, 2010, for a review). Whether these protective effects of sex hormones, and estrogen in particular, also apply to the results of the present study remains speculative.

In sum, this study revealed reduced lateralisation in high-IMP males, as indicated by attenuated LEAs for emotional prosody. Previous studies have shown similar atypical FCAs in schizophrenia, especially in males, suggesting that schizotypy and schizophrenia share sex-specific aspects of atypical functional brain organisation.

Given that research on schizophrenia is often confounded by medication and chronic or recurrent institutionalization (Gooding, Kwapil, & Tallent, 2001), studying healthy individuals high in schizotypy provides a useful approach to enlighten the potential mechanisms underlying cognitive and emotional dysfunctioning in schizophrenia.

Postscript to Chapter 3

The results of atypical lateralisation in IMP, presented in this chapter, refer to IMP as one of the schizotypy dimensions. However, it should be noted that IMP does not represent a specific measure of psychosis proneness. IMP scores have failed to predict differences in clinical psychosis, highest psychotic like experience, or schizotypal dimensional score at follow-up (Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994). In contrast IMP has been related with a broader affective domain of psychosis (Mason & Claridge, 2006). In fact the borderline personality (Claridge & Broks 1984), hypomanic personality (Eckblad & Chapman, 1983), and Eysenck's psychoticism scales (Eysenck & Eysenck, 1975) show high loadings on the impulsive nonconformity factor (Mason & Claridge, 2006).

In keeping with the affective domain, impulsive nonconformity has been related to hypomania. This has been suggested by a 13-year longitudinal study investigating whether high scores in the hypomanic personality scale predicted especially heightened risk to develop BD (Kwapil et al., 2000). It was shown that hypomanic individuals with higher impulsive nonconformity exceeded the remaining hypomanic participants at follow up assessment on the rate of BD. In another study, college university students with high behavioural activation system sensitivity as compared to those with moderate BAS were associated with higher impulsive nonconformity and hypomanic tendencies (Alloy et al., 2006). These findings suggested that in combination, hypomanic and impulsive nonconformity predispose to heightened risk for developing BD.

At the clinical level, impulsive nonconformity has also shown a link with BD. For instance, higher levels of impulsive nonconformity have been reported in 'soft' BD conditions, including diagnoses of 'BD not otherwise' specified and 'cyclothymia', relative to healthy controls (Nusslock, Alloy, Abramson, Harmon-Jones, & Hogan, 2008). Thus, impulsive nonconformity seems to represent an especially sensitive BD related measure. Another longitudinal study examined the rates of conversion to more sever BD (BD type II and I) among individuals with 'soft' BD conditions (Alloy al., 2012). Notably, impulsive nonconformity predicted conversion from

'soft' BD condition to BD type I. Overall, impulsive nonconformity across diverse forms of BD, ranging from hypomanic personality to clinical conditions of 'soft' BD, and BD type I (Alloy et al., 2006, 2012; Kwapil et al., 2000; Nusslock et al., 2008), support a BD continuum. Thus impulsivity may underlie a continuum ranging from more adaptive responses, reflected in short-term benefits, among nonclinical individuals, to negative long-term outcomes affecting full-blown BD.

The findings above are fully consistent with the clinical picture of impulsivity in BD individuals who engage in more risky sexual behaviour, driving behaviour, substance abuse, and aggression (Fulford, Johnson, & Craver, 2008). Indeed a possible explanation for these behavioural tendencies would be that impulsivity in BD results in inability to delay gratification and fulfil long-term goals.

According with these findings and clinical observations, BD seems to involve a symptomatic relationship with impulsivity. This has been supported by indications that those with mania act impulsively (Fulford et al., 2008). This is also reflected on that degree of impulsivity increases as a function of acute manic symptomatology (Lewis, Scott, & Frangou, 2009). However, several studies have consistently showed that impulsivity and BD are still related during euthymia (Ekinci, Albayrak, Ekinci, & Caykoylu, 2011; Lewis et al., 2009; Lombardo et al., 2008; Peluso et al., 2007; Strakowski et al., 2010; Swann, Anderson, Dougherty, & Moeller, 2001; Swann, et al., 2003). For instance, trait impulsivity as measured by the Barratt impulsiveness scale (Patton, Stanford, & Barratt, 1995), is increased in euthymic or minimally symptomatic BD patients (Peluso et al., 2007; Swann et al., 2001, 2003), raising the possibility that impulsivity may be a trait marker for the bipolar illness. Therefore, an association between impulsivity and BD euthymia would indicate that impulsivity is more than the direct expression of mood symptoms in the affected individuals and could have important implications for a better understanding of BD (Peluso et al., 2007). This aspect of BD, affecting a range of BD conditions and supporting a bipolar continuum, in the present study was associated with atypical functional brain organisation, especially compromising right hemisphere functioning. However, the present study investigated impulsive nonconformity in healthy individuals, suggesting that this atypical functional brain organisation can even been linked with the "healthiest" end of the BD continuum. If impulsive nonconformity underlies a BD continuum at the level of the functional brain organisation this should be reflected in euythymic BD involving an intermediate state between normal and acute

mood. Atypical FCAs in euthymic BD have been indirectly supported by neurophysiologic and neuroimaging studies showing right prefrontal activation during emotion perception (Chen et al., 2010; Lee et al., 2010; Morris, Sparks, Mitchell, Weickert, & Green, 2012; Robinson et al., 2008; Wessa et al., 2007). For example, right inferior and middle frontal magnetoencephalographic hyperactivity has been found in euthymic BD patients compared to healthy controls, during an implicit emotional paradigm requiring participants to judge the gender of emotional facial expressions (Lee et al., 2010). The findings of Lee et al. of right hemisphere dysfunction in emotional processing, in line with the present study, may involve a common functional brain organisation relying on BD aspects such as impulsivity. However, it should be noted that EEG and fMRI activation without statistical comparison between hemispheres used in most of the studies above is a highly indirect measure for lateralisation. Thus, the hypothesis of right hemisphere lateralisation in BD euthymia remains speculative and warrants further examination with a more direct measure for lateralisation.

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Chapter 4

The previous chapter demonstrates reduced right hemisphere advantage for emotional processing in men with high hypomanic related traits, as shown by an emotional prosody task. These results suggest a dysfunction in the right hemisphere system for emotional processing related to hypomanic personality traits. Moreover, the deficit in the processing of emotions, typically observed in BD (e.g., Foland et al., 2008; Killgore, Gruber, & Yurgelun-Todd, 2008; Liu et al., 2012; Strakowski et al., 2011; Yurgelun-Todd et al., 2000), implicates a right fronto-temporal network. In fact, this is in line with previous suggestions of a right hemisphere dysfunction in emotional processing in euthymic BD patients (e.g., Chen et al., 2010; Lee, Chen, Hsieh, Su, & Chen, 2010; Morris, Sparks, Mitchell, Weickert, & Green, 2012; Robinson et al., 2008; Wessa et al., 2007). These latter findings have especial implication for identifying a core functional brain organisation of BD, given that the study of euthymic phases provide access to inherent aspects of BD relative to acute phases that are influenced by on going symptomatology. In line with such atypical functional brain organisation in BD, persistent emotion dysregulation in euthymic BD patients has been recently suggested by findings of being "stuck" in the present moment (Gruber, Cunningham, Kirkland, & Hay, 2012). This study involved anticipating future consequences of behaviours and requiring adaptive regulatory capacity. More precisely, the study assessed time perspective with an inventory including items such as, "It doesn't make sense to worry about the future, since there is nothing I can do about it anyway" (p.14). BD patients were associated with more present oriented perspectives and reported a lack of ability to predict the future, which suggested emotional miscalculations of future consequences lead to maladaptive decisions. However, it remains unclear how such disadvantageous decisions perpetuate. Such dysfunctional cycle may be maintained trough intensified internal emotional states associated with an inherent functional brain organisation of BD.

Altered resting state functional connectivity of the amygdala in bipolar disorder

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Abstract

Amygdala dysfunction is perhaps the most common finding in bipolar disorder (BD). However, the involvement of the amygdala in resting state brain networks in BD has not yet been extensively studied. Such an analysis of the functional connectivity of the amygdale with other brain regions during resting state may significantly contribute to the understanding of the putative role of the amygdala in BD. To investigate the amygdala network in BD, we applied a Granger causality analysis to resting state functional magnetic resonance imaging (fMRI) data from 13 euthymic BD patients and 15 age- and gender-matched healthy controls.

Results: The analysis revealed a stronger excitatory influence of right postcentral gyrus (i.e., the primary somatosensory cortex) on the right amygdale in euthymic BD patients as compared to healthy controls. A limitation of the present study concerns the small sample size, which might have prevented the detection of more subtle alterations in amygdala connectivity in BD. Thus future studies with larger sample size will be important to further characterize the amygdala network in BD. The present finding of an atypically stronger right postcentral excitatory influence to the right amygdala in BD might suggest that intensified somatosensory processes, implicating bodily responses associated to felt emotions, might lead to exacerbated motivational dispositions, as observed in the typical symptomatology of BD.

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Introduction

Bipolar disorder (BD) is characterised by a cyclic changing pattern of mood states comprising phases of depressed and elevated mood (American Psychiatric Association, 2000). Clinical symptoms of BD, such as intensified or absent appetitive arousal and motivation for reward, have been linked with maladaptive motivation proposed as a potential endophenotype for BD (Hasler, Drevets, Gould, Gottesman, & Manji, 2006).

A recognised neural substrate for motivation is the amygdala (e.g., Bechara, Damasio, & Damasio, 2003; Everitt, Cardinal, Parkinson, & Robbins, 2003), a brain structure that has been associated with anatomical (e.g., Doty et al., 2008; Hajeck et al., 2009) and functional (Chen, Suckling, Lennox, Ooi, & Bullmore, 2011) abnormalities in symptomatic BD patients. In fact, amygdala dysfunction is probably the most commonly reported finding in functional magnetic resonance imaging (fMRI) studies of BD (e.g., Altshuler et al., 2005; Bermpohl et al., 2009; Foland et al., 2008; for a meta-analysis see Chen et al., 2011). Studies have consistently shown task-related amygdala hyperactivity in BD (Altshuler et al., 2005; Bermpohl et al., 2009; Foland et al., 2008). For example, increased activation of the left amygdala was found in manic BD patients during an emotional face perception task (Altshuler et al., 2005).

It should be noted, however, that the majority of these studies have focused on symptomatic BD patients. Evidence for amygdala dysfunction in euthymic BD patients is less clear (Chen et al., 2011).

One of the few studies that included euthymic BD patients (Chen et al., 2010) reported increased amygdala activation when these patients rated affective intensity of faces. Similarly, other studies found increased amygdala activation in response to fearful (Lawrence et al., 2004) and happy facial expressions (Lawrence et al., 2004; Surguladze et al., 2010) in euthymic BD patients. On the other hand, studies using emotional faces (e.g., Robinson et al., 2008), and a recent meta-analysis (Chen et al., 2011) of fMRI studies using cognitive or emotional tasks did not show any differences in amygdala activation between euthymic BD patients and healthy controls. Thus, the role of the amygdala in BD euthymia, as detected by fMRI task

activation studies, is still unclear, suggesting that other approaches for delineating a potential dysfunction might be indicated.

Resting state fMRI has recently provided an alternative perspective for understanding the function of the brain. Based on brain energy metabolism studies (Raichle, 2006; Raichle & Mintun, 2006), resting state fMRI studies have suggested that the brain shows stable patterns of spontaneous activity in the absence of specific cognitive and/or emotional tasks, and these patterns of spontaneous activity provide an alternative approach to understanding functional brain organisation (Biswal, Yetkin, Haughton, & Hyde, 1995; Fiser, Chiu, & Weliky, 2004; Kenet, Bibitchkov, Tsodyks, Grinvald, & Arieli, 2003; Llinas, 1988; MacLean, Watson, Aaron, & Yuste, 2005). FMRI resting state studies usually apply functional connectivity analyses to investigate distributed brain networks while the brain is "at rest" and not currently involved in a problem solving task. Thus, an analysis of the functional connectivity of the amygdalae with other brain regions during the resting state may significantly contribute to the understanding of the putative role of the amygdala in BD.

To date, very few studies have directly examined functional connectivity of the amygdala at resting-state. Using spatial correlations in a priori defined regions of interests in the pregenual anterior cingulate cortex (ACC), dorsomedial thalamus, pallidostriatum and amygdala, one study found decreased functional connectivity between amygdalae (bilateral) and the pregenual ACC in symptomatic BD patients (manic, n = 6; depressed, n = 5) as compared to healthy controls (Anand, Li, Wang, Lowe, & Dzemidzic, 2009). A further functional connectivity analysis restricted to left ventrolateral PFC and the amygdala showed decreased negative correlations in activation between these areas in BD patients compared to healthy controls (Chepenik et al., 2010). Decreased connectivity between the amygdala and the ventrolateral PFC and ACC may relate to the clinical observation of altered anticipatory reward processing in BD (e.g., Gray 1994). Manic BD patients, on the other hand, did not show differences as compared to healthy controls in functional connectivity between the medial PFC and the amygdala (Chai et al., 2011), suggesting that the medial PFC is not dysfunctionally associated with the amygdala network. Two other resting state studies (Meda et al., 2012; Ongur et al., 2010) applied independent component analyses, a data driven technique which does not use an a priori hypotheses and consequently is not suitable for assessing the role of specific brain regions like the amygdala in resting state brain networks in BD.

Up to now, the few available resting state studies have only examined the interaction of the amygdala and predefined regions of interest, while a whole brain analysis of functional connectivity with the amygdala is still missing. To fully investigate the amygdala network in BD, a Granger causality analysis (GCA) was applied to resting state functional MRI data in euthymic BD patients and healthy controls. GCA provides information on both the timing of neuronal processing and the direction of interaction between network nodes. Thus, this technique allows for the investigation of both afferent and efferent influences within brain networks associated with the amygdala.

Considering previous evidence for amygdala dysfunction in symptom free BD patients (e.g., Altshuler et al., 2000; Brooks, Hoblyn, Woodard, Rosen, & Ketter, 2009), it is hypothesised that euthymic BD patients might display abnormal efferent and afferent amygdala connectivity. Besides decreased functional connectivity of the amygdala with prefrontal regions in BD patients (Chepenik et al., 2010), right parietal areas might be involved because they have previously been linked with motivational-related processes such as the arousal dimension of emotional experience (Heller 1993; Heller, Nitschke, Etienne, & Miller, 1997) and perturbation of this function in mood disorders (Moratti, Rubio, Campo, Keil, & Ortiz, 2008). In fact, BD has been associated with right parietal magnotoencephalographic hyperactivity during an angry facial emotion task, suggesting atypical arousing (Lee et al., 2010; Liu et al., 2012). This effect might have involved the amygdala network, consistent with the prominent role of the amygdala in emotional arousal (e.g., Anderson et al., 2003; Zald, 2003). Thus, the present study applies a whole brain functional connectivity analyses with the left and right amygdalae as seed regions.

Methods

Participants

The study group comprised 28 participants in total: 13 patients with BD (age: 43.08 ± 11.37 years; 7 females) and 15 healthy controls (36.13 ± 12.13 years; 6 females). Groups did not significantly differ in years of education ($t(26) = 0.78$, ns). Patients attending clinical services from Newcastle, North Tyneside, Northumberland NHS Foundation Trust, and Tees, Esk and Wear Valleys NHS Foundation Trust, who fulfilled inclusion criteria, were recruited for the study. Inclusion criteria for patients

were: (1) a diagnosis of BD, type I, according with the Structured Clinical Interview for DSM-IV (SCID-P; First, Spitzer, Gibbon, & Williams, 1995); (2) no current concomitant Axis I disorder; and (3) no history of medical or neurologic conditions that might affect cognitive function. Individuals with a history of anxiety disorders or substance abuse were included in the study, provided that they had not met criteria for a DSM-IV diagnosis in the preceding 6 months.

BD patients were clinically stable outpatients at the time of the study with clinical history of varying length (Number of hospitalizations: 3.00 ± 2.38 (0–7), 30 % of sample had more than five depressive episodes). Current depressive symptoms were assessed using the 17-item Hamilton Rating Scale for Depression (HAM-D; Hamilton 1960). Manic symptoms were assessed with the Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978). Mild depressive symptoms were defined as HAM-D scores of 8 to 13. BD patients were euthymic as a group [HAM-D = 5.38 ± 2.26 (0–8) and YMRS = 4.23 ± 3.72 (0-10)] and based on symptom ratings (HAM-D ≤ 13.43 ± 3.20).

Two patients had a history of alcohol or substance abuse. Eight of the BD patients were taking mood-stabilizing medications; five patients were taking antidepressants. In addition, eight patients received atypical antipsychotic. None of the patients with BD was experiencing psychotic symptoms at the time of the assessment.

Healthy controls were recruited through advertisements placed in local post office, community library and on bulletin boards on the Durham University campus, according to the same exclusion criteria used for patients. In addition, healthy controls had no history of any Axis I disorder and no history of affective disorder or schizophrenia in first-degree relatives. After receiving a complete description of the study, written informed consent was obtained from each participant. The study was approved by the institutional review board of the NHS and Durham University Ethics Advisory Committee. All participants received £20 for participating in the study.

BD patients and healthy controls were right-handed as determined by the Edinburgh Handedness Inventory (Oldfield, 1971). This asymmetry-index ranges from -100 (extreme sinistrality) to +100 (extreme dextrality). The handedness scores for the BD patients (88.39 ± 12.11) and healthy controls (92.69 ± 12.70) did not significantly differ ($t(26) = 0.91$, ns).

Image Acquisition

MRI data acquisition was performed on a PHILIPS Acheiva 3- Tesla scanner (Best, Netherlands). Foam padding and headphones were used to limit head motion and reduce scanner noise. The subjects were instructed to hold still, keep their eyes closed and think about nothing in particular. Hundred and thirty-three functional images were collected axially in 399 seconds by using an echo-planar imaging (EPI) sequence [repetition time (TR)/echo time (TE)/flip angle (FA)/field of view (FOV) = 3000 ms/40 ms/90°/26 cm, resolution = 80 x 79 matrix, slices = 25, thickness = 6 mm, gap = 0 mm, bandwidth = 3889.2Hz/pixel].

Image Processing

Functional images were preprocessed with Statistical Parametric Mapping (SPM8; Wellcome Department of Imaging Neuroscience, London, UK, http://www.fil.ion.ucl.ac.uk) software implemented in MATLAB 7.8.0 (Mathworks Inc., Sherborn, MA). The first five volumes of each run were discarded to ensure signal stabilization. Images were realigned to the first image to correct for head movement and unwarped to correct for the interaction of susceptibility artifacts and head movement. Volumes were then normalised into standard stereotaxic anatomical Montreal Neuro- logical Institute (MNI) space by using the transformation matrix calculated from the first EPI- scan of each subject and the EPI-template. Then, functional images were re-sliced at resolution of 2 x 2 x 2 mm and smoothed by a Gaussian filter of 4 x 4 x 4 FWHM.

Analysis

A Granger causality analysis was performed using REST-GCA (Song et al., 2011) coded in MATLAB (The Mathworks, Natick, MA) and group comparisons on the resulting connectivity maps were conducted in SPM8. The Granger causality analysis was used in order to determine whether the time series from brain regions of interest (bilateral amygdalae) are able to predict or can be predicted from the time series in other brain regions (Granger 1969).

We performed voxel-wise GCA on the signed-path coefficients (Chen et al., 2009) to identify both regions whose time courses predict subsequent amygdala activity

(afferent connections) and regions whose activity is predicted by preceding amygdala activity (efferent connections). The mean time series of the left and right amygdalae, anatomically identified by using a mask derived from the WFU pickatlas (Maldjian, Laurienti, Kraft, & Burdette, 2003), were defined as seed time series. The linear direct influence of the amygdalae on other brain regions and of other brain regions on the amygdala were calculated for every voxel in the brain. Thus, four Granger causality maps (afferent / efferent for the left / right amygdala) were generated for each subject. The order of the autoregressive model was set to 1 using the Schwartz criterion (SC). The six head motion parameters (three for translation and three for rotation) were entered as covariates.

Finally, the resulting GC coefficient maps were subjected to two sample t-tests comparing patients versus healthy controls at a threshold of $p<0.001$. Following a conservative approached the between groups comparisons were masked by the main within group effects. Correction for multiple comparisons to $p<0.05$ was achieved using a cluster extent threshold procedure first described by Slotnick et al. (Slotnick et al., 2003, 2004). As reported in a previous study (Slotnick & Schacter, 2004), the cluster extent threshold procedure relies on the fact that given spurious activity or noise (voxel-wise type-I error), the probability of observing increasingly large (spatially contiguous) clusters of activity systematically decreases (Slotnick & Schacter, 2004). Therefore, the cluster extent threshold can be enforced to ensure an acceptable level of corrected cluster-wise Type I error. For an individual voxel Type I error of $p<0.001$, this procedure identified a cluster extent of 21 contiguous resampled voxels as necessary to correct for multiple voxel comparisons across the whole brain at $p<0.05$.

Results

The GCA revealed significant differences between euthymic BD patients and healthy controls for the afferent connections to the right amygdala only. Efferent connections from the right amygdala and both afferent and efferent connections from/to the left amygdala did not show any significant differences between groups. According to Hamilton et al. (2011), a positive causality can be interpreted as an excitatory effect, whereas negative causalities suggest an inhibitory effect.

Healthy Controls > BD Patients

The left posterior cingulate (BA 24) and bilateral superior temporal gyri (BA 48) as well as the right calcarine fissure/cuneus (BA 18) showed a positive afferent effect on the right amygdala to a significantly greater extent in healthy controls than in euthymic BD patients. In other words, activity in the left posterior cingulate and the superior temporal gyri (bilateral) as well as the calcarine fissure/cuneus predicted subsequent increases in right amygdala activity to a significantly greater extent in healthy controls compared to euthymic BD patients. Results are shown in Table 1 and Figure 1a.

BD Patients > Healthy Controls

The right postcentral gyrus (BA 3) revealed a positive afferent effect on the right amygdala to a significantly greater extent in the euthymic BD patients than in the healthy controls. Thus, activity in the right postcentral gyrus is more associated with subsequent activity of the right amygdala in euthymic BD patients than in healthy controls. Results are shown in Table 1 and Figure 1b.

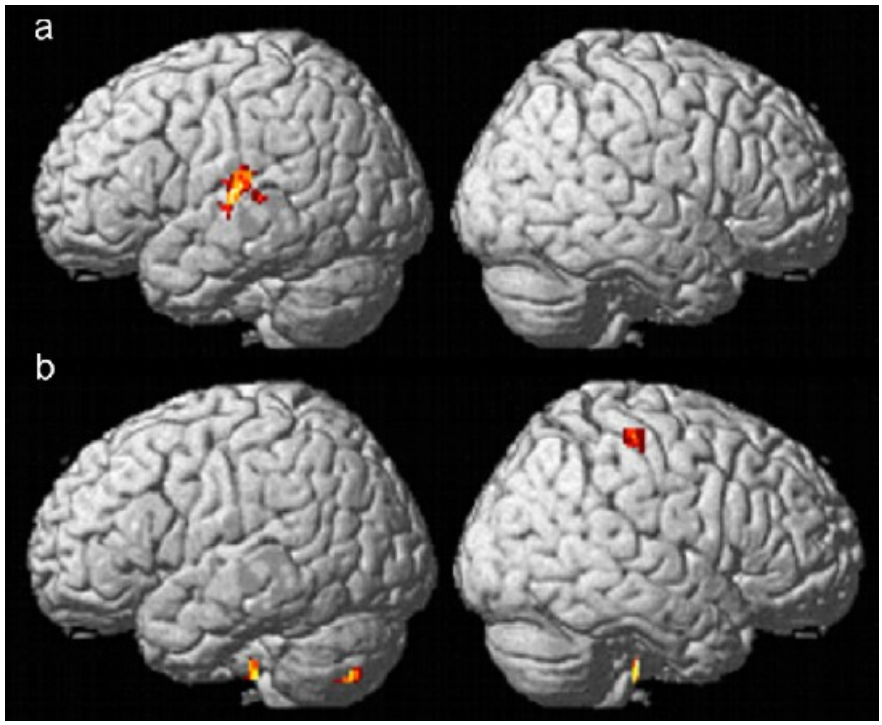

Figure 1a. Stronger afferent connections to the right amygdala in HC compared to euthymic BD. Figure 1b. Stronger afferent connections to the right amygdala in euthymic BD compared to HC.

HC > Euthymic BD	Structure	cluster size	Z score	*x*	*y*	*z*	BA peak
Limbic lobe	L Posterior Cingulate	21	4.34	-6	0	40	24
Temporal lobe	L Superior Temporal	174	4.19	-52	-18	4	48
Occipital lobe	R Calcarine	29	3.84	16	-72	6	18
Euthymic BD > HC							
Parietal lobe	R Postcentral	29	4.66	50	-28	58	3
Subcortical	L cerebelum	24	5.14	-44	-70	-46	-
Brainstem	Brainstem	47	3.75	0	-28	-46	-

Table 1. Differences in afferent connections to the right amygdala in healthy controls and euthymic BD patients. HC = healthy controls; Euthymic BD = euthymic bipolar disorder patients; BA = Brodmann Area; L = Left; R = Right

Discussion

The present study was conducted to contrast resting state brain connectivity of the amygdalae in euthymic BD patients and healthy controls. The amygdale was chosen as a seed region as it is a brain structure that has been associated with both anatomical (e.g., Doty et al., 2008; Hajeck et al., 2009) and functional (Chen et al., 2011) abnormalities in symptomatic BD patients.

For healthy controls, the analyses revealed a stronger afferent influence from left posterior cingulate, bilateral superior temporal gyri and right cuneus to the right amygdale.

The superior temporal gyrus is reported among the auditory areas involved in contamination from scanner background noise (SBN; Gaab, Gabrieli, & Glover, 2007). Comparison of a silent scan protocol, where participants simply listened to SBN, with a different MRI sequence using an auditory task revealed an SBN-induced effect on the superior temporal gyrus (Gaab et al., 2007). The silent protocol additionally revealed SBN contaminated effects in extratemporal areas including cingulate gyrus as well as the cuneus. This might indicate that healthy controls have been more perceptive to SBN.

The present findings showed no difference in connectivity between prefrontal areas and the amygdala between BD patients and healthy controls. It has been suggested, however, that frontal abnormalities might be ameliorated during remission (Chen et al., 2011; Haldane, Cunningham, Androutsos, & Frangou, 2008). For example, a meta-analysis by Chen et al. (2011) on specific mood states demonstrated decreased task-related activity in the inferior frontal gyrus in the state of mania, but not in euthymia. Also, enhanced PFC activity in stable BD patients has been shown after six weeks of lamotrigine treatment (Haldane et al., 2008). Thus, the fact that the BD patients of the present study were euthymic at the time of the study might explain the lack of findings associated with frontal areas.

The analysis of the present study revealed a stronger excitatory influence of right postcentral gyrus (i.e., primary somatosensory cortex) on the right amygdala for euthymic BD patients. Although functional connectivity between the amygdala and the primary somatosensory cortex has not been previously observed, the right lateralisation of both structures is in line with findings showing a dominance of the right hemisphere in emotional processing (e.g., Adolphs, Damasio, Tranel & Damasio, 1996). Furthermore, both the amygdala and the primary somatosensory cortex are both specifically related to the detection of emotional face recognition (e.g., Adolphs, Tranel & Damasio, 1998; Pourtois et al., 2004). For example, similar to impairments in facial emotion recognition following damage of the amygdala (Adolphs et al., 1998), repetitive transcranial magnetic stimulation (rTMS) over the right somatosensory cortex interferes with facial emotion discrimination (Pourtois et al., 2004). However, in contrast to the amygdala, which is rather involved in motivational-related aspects of emotion recognition, such as detection of appetitive objects, filtering perceptions as anticipated rewards, and goal-directed behaviour (Bechara et al., 2003; Baxter & Murray, 2002; Everitt et al., 2003), the right postcentral gyrus, and more generally the right somatosensory cortex, has been related to emotion recognition processes that entail reliance on internal representation of body state (e.g., Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000; Heberlein & Saxe, 2005; Heberlein, Adolphs, Tranel, & Damasio, 2004; Straube & Miltner, 2011).

One of these studies (Adolphs et al., 2000) suggests an involvement of the primary somatosensory cortex in body representation of emotional states. Specifically, this study found that maximal lesion overlap among 108 brain damage patients in the right postcentral gyrus was significantly associated with impaired performance in a facial

emotion recognition task. Also, the right primary somatosensory cortex was engaged in processing emotional compared to neutral pictures in an fMRI study evaluating participants' attentional focus onto the emotional quality of the stimuli and own emotional involvement (Straube & Miltner, 2011). Increasing attention to one's own emotion systematically involved increased brain activation in a subregion of the right primary somatosensory cortex nearly identical to the present findings. Thus these findings not only showed a general overlap in the right primary somatosensory cortex, but more specifically in a similar subregion. Consistent with the function of right primary somatosensory, the authors suggested that the right primary somatosensory cortex might have evoked bodily sensations and that perception of bodily changes might have contributed to the experience of emotion. Another fMRI study found an increase in right somatosensory activity to be associated with detecting the emotional content of faces, rather than detecting the faces' gender (Winston, O'Doherty, & Dolan, 2003). Further support for a role of the right somatosensory cortex in the generation of a body representation associated with felt emotions comes from fMRI studies examining recognition of whole-body emotion expressions (e.g., Heberlein & Saxe, 2005; Heberlein et al., 2004). For example, by using body movements in short dynamic stimuli, one of these studies showed an increased right postcentral activity for emotion compared to personality trait judgments of point light walkers (Heberlein & Saxe, 2005).

Therefore, and in combination with previous fMRI studies, the results of the present study might link somatosensory and amygdala activation by suggesting an afferent pathway from the right primary somatosensory cortex to the amygdala. Given that the present study used resting state instead of a task-dependent approach to examine the functional connectivity of the amygdala, the afferent somatosensory influence to the amygdala may have identified internal body representations associated to the current motivational state.

Although no previous studies have conducted whole brain connectivity analysis of the amygdala network, or assessed functional connectivity between the postcentral gyrus and the amygdala in BD, there is some evidence suggesting that the right somatosensory cortex can be linked to BD symptoms (Keener et al., 2012). For example, an fMRI study revealed activation of the right somatosensory cortex and right amygdala in both euthymic BD patients and healthy controls during facial emotion processing (Keener et al., 2012). The study's task required participants to

label colour flashes that were superimposed on dynamically changing background faces comprising morphs from neutral to angry, sad, fearful, or happy expressions. Notably, the whole brain analysis revealed higher task-related activity in the right somatosensory cortex in euthymic BD patients than in healthy controls. Moreover, region of interest analysis on the amygdala showed significantly higher activity in the euthymic BD patients than in healthy controls, with only right-sided activation after correction for multiple comparisons. The authors suggested that BD patients might have perceived emotional faces as more emotional than healthy controls. Although the results by Keener et al. (2012) did not show direct evidence that the higher activity in the right somatosensory cortex and the amygdala during facial emotion processing are functionally related, the results are in agreement with the proposed role of the right somatosensory cortex in body representation of emotional states (e.g., Adolphs et al., 2000; Heberlein & Saxe, 2005; Heberlein et al., 2004; Straube & Miltner, 2011), which seem to be intensified in BD. Moreover, the findings by Keener et al. (2012) do not clarify whether activity in the right amygdale follows activity in the right somatosensory cortex, as shown in the present study. However, assuming that emotions and motivation are intrinsically related to the physical experience through the own body, one might argue that somatosensory processes associated with the representation of the body may be capable of influencing current motivational states in the amygdala. In BD patients, body representation in the right somatosensory cortex may have intensified current motivational state in the amygdala. Thus this mechanism may explain a core symptomatology of BD consisting on intensified appetitive arousal, expressed as the motivation for seeking rewarding actions of many kinds—toward pleasure, excitement, novelty, social engagement, and physical risk. Although the patients of the present study were not symptomatic, stronger excitatory process from the right postcentral cortex to the right amygdala in euthymic BD patients might have reflected vulnerability for developing motivational symptoms.

Therefore, the present findings involving atypical resting state functional brain organisation associated to motivational and emotional dysregulation in BD euthymia may be particularly important for the understanding of mechanisms predisposing patients to depressed or manic episodes and in identifying biological targets for novel treatments. However it should be noted that more subtle alterations in amygdala connectivity in BD might have passed undetected in the present study considering the

relatively small sample size. Thus future studies with larger sample size will be important to further characterize the amygdala network in BD.

In sum, the present findings specifically reveal an atypical resting state functional brain organisation in BD involving a stronger right postcentral excitatory influence to the right amygdala. Here, it is argued that intensified somatosensory processes, implicating bodily responses associated to felt emotions, might lead to exacerbated motivational dispositions, as observed in the typical symptomatology of BD.

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Chapter 5

In the previous two chapters, selective impairment in the right hemisphere suggested a bipolarity continuum. In Chapter 3 individuals with hypomanic related traits showed a right hemisphere dysfunction in emotion perception. In Chapter 4 euthymic BD patients exhibited atypical connectivity in the amygdala network during resting state, primarily affecting the right hemisphere. Although these two studies examined different aspects of the functional brain organisation of the bipolar spectrum, findings still showed a similarly preserved left hemisphere functioning. This has been shown by Chapter 3 revealing a preserved left hemisphere advantage for linguistic processing, and Chapter 4 demonstrating a spared left amygdala compared to atypical connectivity in the right amygdala during resting state. The BD continuum is further suggested by findings of right lateralised prefrontal fMRI hypoactivation, including orbitofrontal areas (e.g., Foland et al., 2008; Jogia, Haldane, Cobb, Kumari, & Frangou, 2008; Liu et al., 2012; Strakowski et al., 2011), in manic BD patients during emotional processing. Therefore, converging findings of a right hemisphere dysfunction in emotional processing affecting different BD conditions are predictive of a bipolarity continuum. In contrast with the rest of the other BD conditions, the right hemisphere dysfunction in euthymic BD patients, as shown in Chapter 4, implicated resting- rather than emotion-related processes. Given the affective nature of BD one would expect that a bipolarity continuum relate to emotional processing. Thus, in order to test a bipolarity continuum relying on euthymia, as a bridging state between healthy and acute mood, euthymic BD were tested with an emotional prosody DL task, typically revealing a right hemisphere advantage.

Right hemispheric dysfunction in emotional prosody as a risk factor for emotional dysregulation in bipolar disorder euthymia

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Abstract

Bipolar disorder (BD) has been associated with right hemisphere dysfunction, suggesting atypical functional cerebral asymmetries (FCAs) underlying the emotion perception. However, these findings usually come from studies that have not distinguished between symptomatic and euthymic states of BD patients. The aim of the present study is to assess FCAs in emotional prosody and language as a potential risk factor of emotion dysregulation in euthymic BD patients. We evaluated 40 subjects (18 healthy controls and 22 euthymic BD patients) using an emotional prosody dichotic listening (DL) task and a linguistic DL task which have been shown to produce a strong left ear advantage (LEA) and right ear advantage (REA), corresponding to a right and left hemisphere advantage, respectively. Response accuracy rates in the prosodic task revealed a typical LEA for healthy controls which differed significantly from the atypical REA in BD patients. Similarly, correct response times in the prosodic task revealed a significant LEA in healthy controls, whereas no ear advantage was found for the BD patients. Both groups revealed the typical REA in the linguistic task. Atypical FCAs and right hemispheric dysfunction in emotional prosody in euthymic BD patients is in line with previous studies on emotion perception, indicating a contribution of the right hemispheric fronto-amygdala network in emotion dysregulation. In view of recent research, the present results suggest a key role of right hemispheric dysfunction in emotional prosody in euthymic BD patients as a risk factor in emotional dysregulation and hypereactivity to even emotionally neutral situations.

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Introduction

Bipolar disorder (BD) is a highly dynamic disorder with a cyclic pattern of mood states ranging from hypomania and moderate depression to severe mania or depression with psychotic features, as well as mixed states (Müller-Oerlinghausen, Bauer, & Berghofer, 2002). BD is associated with dysfunction of emotion regulation (Phillips, Drevets, & Ladouceur, 2008), which involves the initial steps of the perception of information eliciting emotional arousal. Dysfunctional emotion regulation in BD has been shown by several behavioural studies reporting impaired labelling or matching of facial emotions during manic and depressive mood states (Getz, Shear, & Strakowski, 2003; Lembke & Ketter, 2002; McClure, Hoberman, Leibenluft, Pine, & Pope, 2003; Yurgelun-Todd et al., 2000). Similarly, deficits in emotional processing in BD during both depressive and manic episodes have been found with the emotional Stroop task, in which BD patients showed longer response times in colour naming of depression-related words as compared to neutral words. This finding has been explained by difficulties of BD patients in suppressing responses to distracting emotional word information, while selectively maintaining attention on the colour of the word (French, Richards, & Scholfield, 1996; Kerr, Phillips, & Scott, 2005; Lyon, Bentall, & Startup, 1999).

Consistent with these findings, BD has been associated with structural abnormalities in right frontal regions, which are also implicated in emotion regulation (Bora, Fornito, Pantelis, & Yucel, 2010; Selvaraj et al., 2012). This has been shown by converging findings from two recent meta-analyses of voxel-based morphometry studies in BD patients revealing reduced grey matter volume in right inferior frontal areas, encompassing the ventrolateral prefrontal cortex (Bora et al., 2010; Selvaraj et al., 2012). Although less consistent, BD has also been associated with reduced amygdala volume, especially in the right hemisphere (e.g., Rosso et al., 2007).

Emotional dysregulation in BD has also been linked to atypical hemispheric asymmetries on the functional level (i.e., functional cerebral asymmetries, FCAs) as indicated by right hemisphere dysfunction of emotion perception (Foland et al., 2008; Killgore, Gruber, & Yurgelun-Todd, 2008; Liu et al., 2012; Strakowski et al., 2011; Yurgelun-Todd et al., 2000). This is in accordance with the predominant involvement of the right hemisphere in processing emotions (Adolphs, Damasio, & Tranel, 2002), especially negative emotions (Najt, Bayer, & Hausmann, 2012a).

Atypical FCAs in emotion perception have frequently been associated with symptomatic BD phases, involving right orbitofrontal and ventrolateral prefrontal areas (Foland et al., 2008; Killgore et al., 2008; Liu et al., 2012; Strakowski et al., 2011; Yurgelun-Todd et al., 2000). Manic BD patients, for example, showed decreased right inferior orbitofrontal activation during passive viewing of a series of black and white fearful facial expressions (Killgore et al., 2008). These findings suggest that dysfunction of orbitofrontal and prefrontal areas in the right hemisphere underlies deficits in emotion perception in BD patients during manic episodes.

Several other neuroimaging studies found that emotion processing in BD patients is associated with abnormal activation in the fronto-amygdala network, especially in the right hemisphere (e.g., Blumberg et al., 2005; Foland et al., 2008; Killgore et al., 2008; Kim et al., 2012; Pavuluri, Harral, Passarotti, & Sweeney, 2009; Liu et al., 2012; Strakowski et al., 2011; Yurgelun-Todd et al., 2000). For example, Blumberg et al. (2005) found an increase in right amygdala activation in response to happy faces in depressive BD patients. These findings converge with many other studies showing atypical activation in the right hemisphere fronto-amygdala network of BD patients during emotion perception (e.g., Blumberg et al., 2005; Foland et al., 2008; Killgore et al., 2008; Kim et al., 2012; Pavuluri et al., 2009; Liu et al., 2012; Strakowski et al., 2011; Yurgelun-Todd et al., 2000).

It should be noted, however, that the majority of these studies did not differentiate between symptomatic and euthymic BD patients. Therefore, at present it cannot be concluded whether right hemisphere dysfunction is a feature of BD patients during symptomatic and/or euthymic states. If right hemisphere dysfunction can consistently be found in the latter group, atypical FCAs might be a valuable marker for BD regardless of mood episodes.

A few studies that did differentiate between symptomatic and euthymic BD patients suggest that right hemisphere dysfunction during emotion perception can also be found in euthymic BD patients (e.g., Chen et al., 2010; Keener et al., 2012; Morris et al., 2012). For example, a recent fMRI study (Keener et al., 2012) on emotional face perception in euthymic BD patients found an increase in activation of the right amygdala, especially in response to happy faces. Similarly, right hemisphere dysfunction in BD euthymia during emotion perception has also been found by others (Chen et al., 2010; Robinson et al., 2008; Wessa et al., 2007). Whereas one of these studies revealed increased activation in the right amygdala and right orbitofrontal

cortex (Chen et al., 2010), two other fMRI studies found an atypical increase in right prefrontal activation (Robinson et al., 2008; Wessa et al., 2007).

The majority of fMRI studies have investigated emotional processing in the visual domain, probably because of the disrupting background noise during MRI scanning. However, an increasing number of fMRI studies in healthy subjects have investigated the processing of emotional prosody, which consists of the perception of emotional information that is conveyed by tone of voice. These studies indicate that processing of emotional prosody relies on areas within the right hemisphere including the prefrontal cortex (Buchanan et al, 2000; George et al, 1996), anterior auditory cortex (Buchanan et al, 2000), superior temporal gyrus (Wildgruber, Ackermann, Erb, Grodd, & Pihan, 2002; Wildgruber et al., 2005; Zatorre, 2001; Zatorre, Evans, Gjedde, & Meyer, 1992; Zatorre, Evans, & Meyer, 1994), amygdala and orbitofrontal areas (Grandjean et al., 2005; Sander & Scheich, 2001; Wildgruber et al., 2005).

There are only a few studies that have investigated the perception of emotional prosody in BD patients (e.g., Mitchell, Barry, Cruttenden, Elliott, & Woodruff, 2004). Similar to visual studies, Mitchell et al. (2004) also found a right hemisphere dysfunction in BD patients during passive listening to non-semantic, emotionally spoken words. In contrast to previous studies, however, a *decrease* in the activation of the right inferior frontal gyrus and the right superior temporal gyrus was found.

Although the vast majority of fMRI findings suggest that dysfunction in emotion perception of euthymic BD patients mainly involves cortical areas in the right hemisphere, functional differences between the left and right hemisphere have not been investigated directly. Conclusions drawn on atypical FCAs as a neural marker of BD euthymia are primarily based on the isolation of clusters that pass a predetermined activation threshold in one hemisphere and not the other (Herrington et al., 2010). So far, only Mitchell et al. (2004) included direct statistical comparisons between BOLD signals from cortical areas of both the left and right hemispheres in BD patients during processing of emotional prosody. Again, however, this study did not assess patients' mood states during the time of testing. Thus, it remains unclear whether these findings apply to symptomatic BD patients, euthymic BD patients, or both.

A simple and reliable technique to study FCAs in processing speech and emotional prosody is the dichotic listening (DL) paradigm (Hugdahl, 2000; Voyer & Flight, 2001). In DL a participant is simultaneously presented with two different auditory stimuli (usually speech) separately to each ear via headphones. After each trial,

participants are asked to repeat the stimulus (usually one) they have identified. The DL paradigm typically shows a better reproduction of speech stimuli presented to the right ear (right ear advantage, REA, Hugdahl et al., 1999). Due to the predominantly contralateral projection in the auditory system (Kimura, 1967), the REA has been interpreted as indicating a left hemisphere advantage in language processing. This has been confirmed by fMRI studies showing significant correlation between the degree of REA and left-lateralised brain activation (e.g., Fernandes, Crawley, Logan, McAndrews, & Smith, 2006; van Ettinger-Veenstra et al., 2010). Following the same logic, a left ear advantage (LEA) generally found for non-verbal stimuli, such as complex tones (e.g., Sidtis, 1981) and emotional prosody (e.g., Bryden & MacRae, 1989; Grimshaw, Covell, Johnson, & Kawasny, 2003), indicates right hemisphere specialisation.

In line with a right hemisphere dysfunction in BD, two DL studies in symptomatic BD patients found a reduced LEA for processing complex tones (Bruder et al., 1989, 1994). Bruder et al. (1994) tested BD patients during manic and again during euthymic states using the complex tone DL task, in which participants were asked to discriminate pitch in a dichotic pair of complex tones. Here, BD patients revealed a reduced LEA during mania, in contrast to the expected LEA in healthy controls. During euthymia, however, LEA was preserved, suggesting that a reduced right hemisphere advantage for the processing of complex tones is specific to symptomatic BD patients. Similarly, Bruder et al. (1989) found a reduced LEA in melancholic depressive BD patients in the complex tone DL task. Overall these findings suggest that symptomatic BD patients show atypical FCAs, due to right hemisphere dysfunction of processing pitch. It is important to note, however, that pitch is a fundamental auditory feature of emotional prosody (Perrot, Aversano, & Chollet, 2007). Therefore, impaired pitch perception could have driven the right hemisphere dysfunction in BD patients during processing of emotional prosody in Mitchell et al.'s (2004) study.

Another DL study assessed FCAs of speech processing in BD patients during manic episodes with psychotic symptoms and euthymic episodes using verbal digits as stimuli (Kaprinis, Kandylis, Kaprinis, Karavatos, & Nimatoudis, 1995). The authors found that, similar to healthy controls, manic BD patients after recovery (i.e., euthymia) showed the expected REA. However, during manic states, the same BD patients showed an LEA, indicating an atypical right hemisphere advantage in speech

processing. The authors hypothesised that this result may be explained by hyperactivation of the right hemisphere in symptomatic BD patients, which has been found in several previous fMRI studies as mentioned above. This explanation, however, seems rather unlikely because the same studies have shown that hyperactivation in the right hemisphere of BD patients is clearly dysfunctional. Overall, DL studies suggest that symptomatic BD patients show atypical FCAs due to right hemispheric dysfunction. However, this needs to be confirmed in euthymic BD patients. Interestingly, none of these DL studies assessed emotional prosody in BD and DL findings are partly conflicting for predominantly left hemispheric functions, such as speech processing.

Therefore, the present study aims to investigate euthymic BD patients with prosodic and linguistic DL tasks, which have previously been shown to produce a robust LEA and REA, corresponding to right and left hemisphere advantages, respectively (Grimshaw et al., 2003). Based on the assumption that right hemisphere dysfunction can occur independently of manic or depressive mood states in BD, it is hypothesised that euthymic BD patients will show a reduced LEA in processing emotional prosody, whereas the REA for linguistic processing will be preserved.

Methods

Participants

Twenty-two patients (13 women) with BD (Age: 44.59 ± 9.97 years) were recruited from the Northumberland NHS Foundation Trust, and the Tees, Esk and Wear Valleys NHS Foundation Trust. All the individuals fulfilled the following inclusion criteria: (1) a diagnosis of BD, type I, according with the Structured Clinical Interview for DSM-IV (SCID-P; First, Gibbon, Spitzer, & Williams, 1995), (2) no current concomitant Axis I disorder, and (3) no history of medical or neurologic condition. Individuals were also excluded if they met the DSM-IV diagnosis for anxiety disorders or substance abuse within the preceding six months. Bipolar patients were clinically stable outpatients at the time of the study. The current depressive symptoms were assessed using the 17-item Hamilton Rating Scale for Depression (HAM-D; Hamilton 1960). The manic symptoms were assessed with the young mania rating scale (YMRS; Young, Biggs, Meyer, & Ziegler, 1978).

As a group [HAM-D = 3.05 ± 1.98 (0–7) and YMRS = 5.18 ± 4.23 (0-10)] and based upon symptom ratings (HAM-D ≤ 7, YMRS ≤ 10), BD patients were euthymic on the day of the study. Previously anxiety symptoms were present in three of the patients. Five patients had a history of alcohol or substance abuse. Fifteen of the bipolar patients were taking mood-stabilising medications; eight patients were taking antidepressants. In addition, twelve patients received atypical antipsychotics. None of the BD patients experienced psychotic symptoms at the time of the assessment.

Eighteen healthy controls (Age: 45.11 ± 7.5 years; 9 women) were recruited through local announcements (e.g., local post office, community library, Durham University, etc.). Control participants were matched for age, sex, and education and had no history of any Axis I disorder and no history of affective disorder or schizophrenia in first-degree relatives.

Patients and controls were right-handed as determined with the Edinburgh Handedness Inventory (Oldfield, 1971). The asymmetry index provided by this test is calculated using the following formula: ((R-L)/(R+L)) x 100, resulting in values between -100 and +100. This range describes the continuum from extreme sinistrality to extreme dextrality. The handedness scores for patients (88.99 ± 12.51) and controls (91.67 ± 9.85) did not significantly differ ($t(38) = .74$, n.s.).

All participants were compensated for participating in the study. The study was approved by the regional ethics committee from the NHS and Durham University Ethics Advisory Committee and was performed in accordance with the Helsinki Declaration of 1975. After receiving a complete description of the study, written informed consent was obtained from each participant.

Procedure and Materials

The DL paradigm was identical to that described by Grimshaw et al. (2003, see for more details). The experiment consisted of a linguistic (word identification) and a prosodic DL task. The linguistic task required participants to recognise a particular word target, and typically generates a REA corresponding to the left hemisphere. The prosodic task required participants to recognise a particular emotional tone of voice, and this task typically generates a LEA corresponding to the right hemisphere. The stimuli set for both tasks consisted of four two-syllable words: “bower”, “dower”, “power”, and “tower”, each spoken by a male voice in angry, happy, neutral, and sad

tones of voice (Bryden & MacRae, 1989). Both tasks consisted of four blocks of 72 trials, for a total of 288 trials (excluding 16 additional practice trials). Word target and voice target, as well as block order, were counterbalanced across participants. Orientation of supraaural headphones with circumaural cushions was reversed across participants.

Participants were instructed to listen either for a word target or voice target, and respond as quickly and accurately as possible to whether or not they heard the target in either ear using the index and middle fingers on the "1" (present) and "2" (absent) keys of a computer keyboard. Each word or tone of voice was present in 50% of the trials, 25% in the left ear and 25% in the right ear. Participants responded to both the word target and the voice target for two consecutive blocks. The experiment was controlled by E-Prime (Psychology Tools Inc., Pittsburgh, PA) on a desktop PC. Response times (RT) and accuracy were recorded as dependent measures.

Results

Accuracy

The accuracy data was subjected to a mixed analysis of variance (ANOVA), with Task (linguistic/prosodic) and Ear (left/right) as within-subjects factors, and Sex and group (patients/controls) as between-subjects factors. The ANOVA revealed a significant Ear by Task interaction, $F(1, 36) = 27.90$, $p < 0.001$, $\eta^2 = 0.44$, indicating the expected REA and LEA for the linguistic and prosodic tasks respectively. Moreover, there was an interaction between Ear and Group, $F(1, 36) = 6.67$, $p < 0.05$, $\eta^2 = 0.16$. The 3-way interaction between Task, Ear, and Group was also significant, $F(1, 36) = 27.51$, $p < 0.001$, $\eta^2 = 0.16$. To investigate the nature of the 3-way interaction, accuracy scores for the linguistic and prosodic tasks were subjected to two separate ANOVAs. The analyses revealed a significant interaction between Ear and Group for the prosodic task ($F(1, 36) = 25.70$, $p < 0.001$, $\eta^2 = 0.42$), but not for the linguistic task ($F(1, 36) = 1.50$, n.s.). Post-hoc paired *t*-tests (Bonferroni) revealed a significant LEA for the prosodic task in healthy controls ($t(17) = 5.66$, $p = 0.0003$). In contrast, BD patients revealed an atypical REA in the prosodic task which approached significance ($t(21) = -2.22$, $p = 0.04$, not significant after Bonferroni correction). For the linguistic DL task, both healthy controls ($t(17) = -3.56$, $p = 0.002$) and BD patients ($t(21) = -3.25$, $p = 0.004$) demonstrated significant REAs. Post-hoc unpaired

t-tests revealed significantly higher accuracy rates for the left ear in healthy controls than BD patients ($t(38) = 3.66$, $p = 0.0008$). In contrast, accuracy for the right ear was significantly lower in healthy controls than for BD patients in this task ($t(38) = -2.58$, $p = 0.014$). There were no significant group differences in left and right ear accuracy scores for the linguistic task (all *ts*< -0.74, n.s.). Mean accuracy is shown in Figure 1.

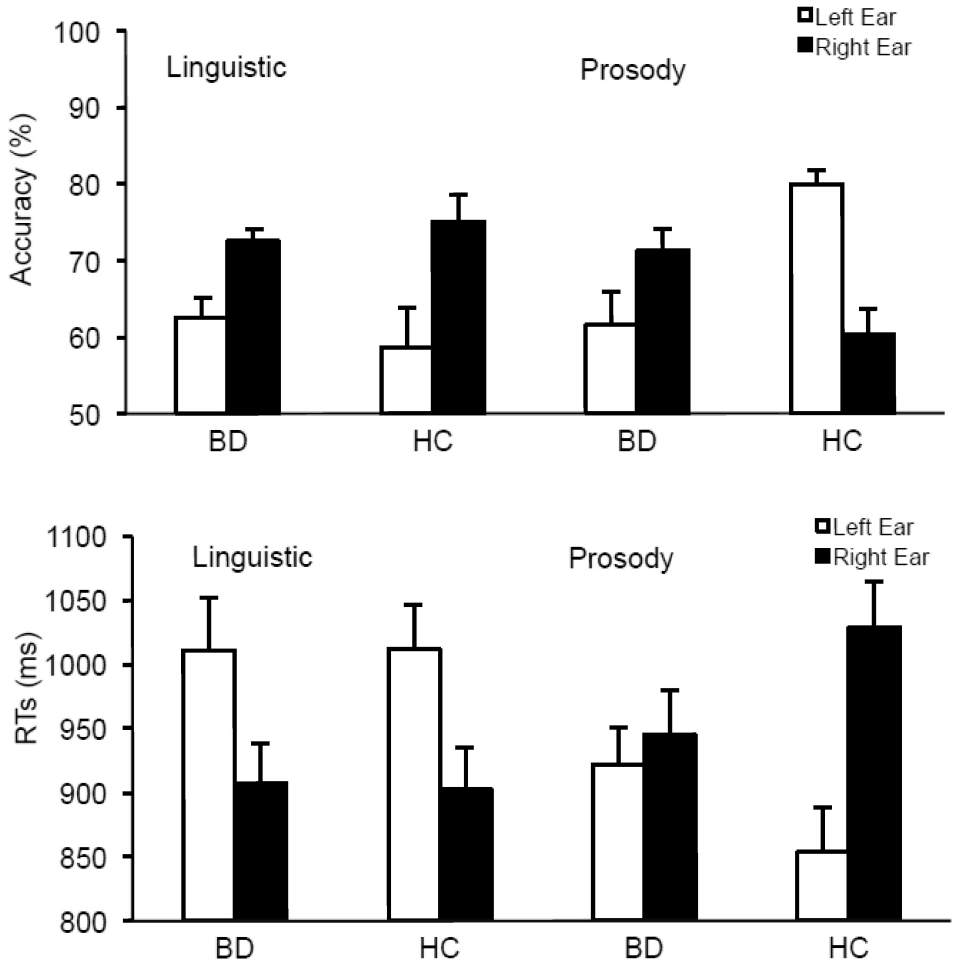

Figure 1. Correct responses (%) and response times (ms) to stimuli presented to the left ear (white bars) and to the right ear (black bars) for bipolar disorder (BD) patients and healthy controls (HC). The results for the linguistic DL task are shown on the left and those for the prosodic DL task are shown on the right.

Response times (RTs)

The corresponding analysis for median RTs also revealed a significant Task by Ear interaction, ($F(1, 36) = 35.06$, $p < 0.001$, $\eta^2 = 0.49$) with an LEA in the prosodic DL

task and an REA in the linguistic DL task. The interaction between Task, Ear, and Group was also significant, ($F(1, 36) = 5.24$, $p < 0.05$, $\eta^2 = 0.13$). Similarly to the accuracy data, median RTs were further subjected to two separate ANOVAs, one for each task. Again, the Ear by Group interaction was only significant in the prosodic DL task ($F(1, 36) = 8.53$, $p < 0.01$, $\eta^2 = 0.19$) and not the linguistic version ($F(1, 36) = 0.13$, n.s.). Post-hoc paired *t*-tests revealed a significant LEA for the prosodic task in healthy controls ($t(17) = -4.70$, $p = 0.0002$), but not in BD patients ($t(21) = -0.65$, n.s.). In contrast, both healthy controls ($t(17) = 3.16$, $p < 0.006$) and BD patients ($t(21) = 2.62$, $p = 0.016$) revealed significant REAs for the linguistic task. Post-hoc unpaired *t*-tests did not reveal any significant group differences in RT for the left and right ear in both the linguistic and prosodic tasks (all $ts < 1.65$, n.s.). Mean response times are shown in Figure 1.

Discussion

The results of the present study revealed atypical FCAs in emotional prosody in euthymic BD patients for both accuracy and RT. For the processing of emotional prosody, healthy controls and euthymic BD patients differed significantly, with the former showing a LEA and the latter a REA. In contrast, the linguistic task revealed pronounced REAs in both groups. As predicted, the results suggest a right hemisphere dysfunction in euthymic BD patients for detecting emotional prosody.

The LEA for the prosodic DL task and REA for the linguistic DL task in healthy controls is in accordance with several previous findings (Bryden & MacRae, 1989; Grimshaw et al., 2003; Najt et al., 2012a) and further supports the reliability of the DL paradigm. The present finding of a significant REA in emotional prosody in euthymic BD patients is in strong agreement with a general right fronto-temporal dysfunctioning in these patients (e.g., Blumberg et al., 2005; Foland et al., 2008; Killgore et al., 2008; Kim et al., 2012; Liu et al., 2012; Pavuluri et al., 2009; Strakowski et al., 2011; Yurgelun-Todd et al., 2000). The results of the current study are especially in line with Mitchell et al. (2004), who found atypical low activation in the right hemisphere (i.e., inferior frontal and superior temporal gyri, and amygdala) of BD patients, as compared to healthy controls, while listening to emotional prosody. This finding has been interpreted by the authors as a reduced capacity to process emotional prosody in BD patients. However, given that Mitchell et al. (2004) did not

control for mood state, it was unclear whether atypical functional brain organisation, and right hemispheric dysfunction in particular, only occurs during manic/depressive mood states or also applies to euthymic states in BD patients.

As already mentioned above, previous DL studies in manic and depressive BD patients also found a reduced LEA in the non-emotional complex tone task – a paradigm that typically reveals a strong LEA (Bruder et al., 1989, 1994). Interestingly, however, euthymic BD patients have shown a preserved right hemisphere advantage in this task (Bruder et al., 1994). These findings suggest severe right hemisphere dysfunction of symptomatic BD patients in processing basic auditory information (i.e., pitch) *and* emotional prosody, whereas right hemispheric functioning seems to selectively affect emotional processing in BD euthymia. This is compatible with the observation of largely preserved general intellectual and executive functions as well as selective attention in euthymic (Martínez-Arán et al., 2000; Quraishi & Frangou, 2002) in contrast to symptomatic BD patients (Addington & Addington, 1997; Dixon, Frith, Kravariti, McGuire, & Murray, 2004; Fleck, Sax, & Strakowski, 2001).

The typical REA in the linguistic DL task in euthymic BD patients of the present study was virtually identical to healthy controls. This parallels previous DL findings in symptomatic BD patients who also showed typical REAs in BD patients during mania and depressive mood states (e.g., Bruder et al., 1989, 1992, 1994). Bruder et al. (1994), tested manic BD patients and found the expected REA in a consonant-vowel DL task. A finding which was similar to two earlier studies by Bruder et al. (1989, 1992) examining depressive BD patients with the consonant-vowel DL task. So far, there has only been one DL study (Kaprinis et al., 1995) that reported a reduced REA in a verbal DL task in manic BD patients with psychotic symptoms (i.e., mainly delusions), suggesting a left hemisphere involvement, possibly related to the presence of psychosis. Overall, these findings suggest that cortical functions that rely more on the left hemisphere, such as verbal abilities, are less affected in symptomatic *and* euthymic BD patients.

It has been claimed previously that the underlying mechanisms in BD may also indicate interhemispheric abnormalities (Chepenik et al., 2010; Kaprinis et al., 1995; Pettigrew & Miller, 1998; van Dyck, Blumberg, & Pittman, 2012; Wang et al., 2008). Kaprinis et al. (1995) proposed a reciprocal inhibitory relationship between the two hemispheres, where changes in activation of one hemisphere should result in opposite

changes in the contralateral hemisphere. Consequently, a reduced right hemisphere advantage (and increase in right hemisphere activation) in euthymic BD patients should be accompanied by an increase in left hemisphere advantage in a verbal task. Similarly, Pettigrew and Miller (1998), using binocular rivalry, which is thought to reflect competition between monocular neurons within the primary visual cortex, suggest that BD is associated with a dysfunctional state of interhemispheric switching. Thus, mood shifts in BD are explained in terms of slow switching, predisposing to unrelieved left hemisphere activation in mania, or unrelieved right hemisphere activation in depression. However, the atypical FCAs found in the present study appeared only in the right hemispheric prosody task, whereas the left hemisphere advantage for the linguistic task was not affected. This makes it rather unlikely that interhemispheric abnormalities can account for atypical FCAs, at least in euthymic BD patients, and strongly suggests that the underlying mechanism relates specifically to a dysfunction of the right hemisphere.

A recent fMRI study (Morris, Green, Mitchell, Sparks, & Weickert, 2012) suggests that the right hemispheric dysfunction in euthymic BD patients may in fact be the key mechanism involved in inefficient inhibitory top-down control, and thus the inability in suppressing hypersensitivity to emotional salience. After manipulating the emotional state of euthymic BD patients by guided instructions of ‘increasing’, ‘decreasing’ or ‘maintaining’ the subjective affect conveyed by the negative pictures, Morris et al. (2012) found an increased activation in the ventrolateral prefrontal cortex and amygdala in the right hemisphere, as well as a dysfunctional cortico-limbic coupling.

Another recent study (M’Bailara et al., 2009) also suggests that euthymic BD patients display emotional hyperreactivity, mostly evidenced in emotionally neutral situations. The authors conclude that this observation can probably be linked to emotional dysregulation and may also be interpreted as a potential endophenotype and/or risk factor for BD. Further, the authors conclude that, “this trait may be responsible for vulnerability to minor stressful events in everyday life” (p. 63). The findings of the present study suggest that this trait of vulnerability probably relates to the fronto-temporal network of the right hemisphere.

An atypical FCA for emotional prosody, and right hemisphere dysfunction in particular, has also been suggested as a risk factor for emotional dysregulation in healthy subjects. By using the same prosodic and linguistic DL tasks as in the present

study, a similarly reduced LEA in the prosodic task has been found in healthy males who are high in impulsive non-conformity, a hypomanic-related personality trait (Najt et al., 2012b). Healthy subjects with low impulsive non-conformity scores showed the typical LEA in this task. In addition, a typical REA was found in the linguistic task irrespective of this personality trait. The similarities in FCAs between the euthymic BD patients of the present study and healthy men high in impulsive non-conformity suggests that BD-related personality traits can already be linked to right hemispheric dysfunction in emotional prosody, even when not exceeding the pathological level.

In sum, BD patients showed atypical FCAs consisting of a significantly reduced LEA in emotional prosody, which indicates a dysfunction of the right hemisphere in emotion processing. Left hemispheric functioning seems not to be affected in these patients. The results further indicate that the current mood state in BD patients does not account for these findings, because atypical right hemisphere functioning was present in patients that were symptom free during the time of testing. Given that similar findings have been recently reported in healthy men with relatively high hypomanic-related personality traits, the results further suggest that atypical FCAs in predominantly right hemisphere functions are a characteristic of the whole bipolar spectrum. Finally, the present study supports the view that the DL paradigm is a useful tool to characterise the functional brain organisation as a risk factor in various neuropsychiatric disorders.

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Chapter 6

As shown in previous chapters, an emotional brain network involved in BD, implicated atypical organisation of the right fronto-temporal network. This is in line with clinical observations of emotion lability, hyperreactivity, and dysregulation in BD patients. Moreover, the right hemisphere system especially implicated in emotional processing as shown by Chapter 2 in healthy controls, was associated with a selective vulnerability to emotion dysregulation in all the BD studies. The DL studies showing a reduced right hemisphere performance for the detection of emotional prosody in BD patients and people with hypomanic traits also supported this assumption. In contrast, a spare left hemisphere functioning in linguistic processing was found in BD patients and individuals with hypomanic traits. Thus these findings suggest that the right hemisphere involvement in BD is restricted to emotional processing.

However, none of these studies have in fact evaluated the possibility that the right hemisphere dysfunction also affects other psychological processes not associated to emotion. Addressing this question requires a right-lateralised task drawing heavily on non-emotional processes. Taken in consideration that mood influences FCAs (Compton & Levine, 1997; Papousek & Schulter, 2002; Tomarken, Davidson, & Henriques, 1990; Wheeler, Davidson, & Tomarken, 1993) the evaluation of right hemisphere lateralisation of non-emotional processes should focus in BD euthymia rather than symptomatic states.

The present chapter investigates euthymic BD patients using a visual line bisection-task typically revealing right hemisphere dominance in visuospatial attention. The visual line bisection is of particular interest for this study given that is a reliable laterality measure reflecting right hemisphere dominance for a non-emotional function. Moreover, this task has been shown to be especially sensitive for detecting atypical functional brain organisation across different neuropsychiatric disorders (Manly, Cornish, Dobler, Grant, & Hollis, 2005; Rolfe, Hamm, & Waldie, 2008; Sheppard, Bradshaw, Lee, & Mattingley, 1999; Waldie & Hausmann, 2010).

Right fronto-parietal dysfunction underlying spatial attention in bipolar disorder

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Abstract

Although the neural underpinning of bipolar disorder (BD) is still unknown, recent research suggests that the right fronto-parietal cortex is particularly affected in BD patients. If this were true, we would expect atypical functional cerebral asymmetries (FCAs) in allocation of visuospatial attention. To test this hypothesis, euthymic BD patients and age- and gender-matched healthy controls were compared on the visual line-bisection task, a reliable measure of visuospatial attention, associated with right parietal function. Line bisection performance (i.e., absolute and directional bias) was compared between groups as a function of response hand, scanning direction and line position. The results showed a typical hand-use effect in healthy controls involving a larger leftward bias (i.e., pseudoneglect) with the left hand than with the right hand. Although euthymic BD patients did not differ from healthy controls in the overall accuracy (i.e., absolute bias), they differed significantly in the directional line bisection (LB) bias. In contrast to healthy controls, BD patients did not significantly deviate from the veridical center, regardless which hand was used to bisect horizontal lines. This finding indicates an atypical FCA in visuospatial attention in BD euthymia, supporting the idea of a dysfunction especially in the right fronto-parietal cortex.

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Introduction

Bipolar disorder (BD) is a common mental illness with an overall lifetime prevalence of about 1% in the general population (Müller-Oerlinghausen, Berghofer, & Bauer, 2002). Typically, BD is characterised by a cyclic pattern of mood states that includes phases of depressed and elevated mood, as well as euthymic periods. The clinical presentation of BD ranges from hypomania and moderate depression to severe mania or depression with psychotic features, as well as mixed states (Müller-Oerlinghausen et al., 2002).

The neural underpinning of BD remains unclear. However, a right hemisphere involvement in BD has been suggested by findings of decreased gray matter volume in right prefrontal and parietal lobes (Adler et al., 2005; Lyoo et al., 2004) as well as cortical thinning in right superior parietal areas (Lyoo et al., 2006). In addition, neuroimaging and neurophysiological studies revealed atypical functional brain organisation, particularly involving the right hemisphere rather than the left (e.g., Grisaru, Belmaker, Chudakov, & Yaroslavsky, 1998; Rubinsztein et al., 2001; Townsend, Altshuler, Bookheimer, Foland-Ross, & Sugar, 2010). For example, a positron emission tomography (PET) study using a decision-making task, where participants were asked to choose between a red and a blue box to find a token, showed a decreased right superior frontal activation in manic BD patients compared to healthy controls (Rubinsztein et al., 2001). Also, fMRI activation during an n-back task where subjects had to identify letters two positions back in a letter sequence, replicated prior findings of bilateral dorsolateral prefrontal cortex (PFC) and parietal regions in healthy controls, whereas BD patients revealed reduced right parietal activation (Townsend et al., 2010). Moreover, a study (Grisaru et al., 1998) investigated the clinical properties of repetitive transcranial magnetic stimulation (rTMS) applied over the left and right PFC. The results showed that manic symptoms of BD patients significantly improved after rTMS over the right PFC compared to BD patients receiving rTMS of the left PFC. These findings could also have implications for atypical FCAs (i.e., right hemisphere dysfunction) underlying acute mood in BD.

Atypical FCAs particularly affecting frontal and parietal areas of the right hemisphere in BD have also been shown by a dichotic listening (DL) click detection task assessing selective attention (Bruder, Berger-Gross, Davies, Quitkin, & Sutton,

1981; Yozawitz et al., 1979). This particular DL paradigm involves the presentation of clicks simultaneously to the right and left ear. FCAs in selective attention using the DL click detection task is normally reflected by a better reproduction of a click previously presented to the left ear (i.e., left ear advantage, LEA), suggesting a right hemisphere advantage in healthy controls (Bender & Diamond, 1975). BD patients, however, revealed a significant right ear advantage in this task (Bruder et al., 1981; Yozawitz et al., 1979), suggesting atypical left hemisphere superiority in selective attention. The authors therefore conclude that this atypical functional brain organisation in BD patients may have resulted from right hemisphere dysfunction.

In BD, right hemisphere dysfunction involving visuospatial functioning, has also been shown by visual half-field studies using the dot enumeration task (Bruder et al., 1989). Specifically, BD patients, in contrast to healthy controls, failed to show the expected left visual field (right hemisphere) advantage for reporting the number of dots presented within visual half-fields (Bruder et al., 1989, 1992, 1994). Moreover, an event-related potential (ERP) study replicated the reduced left visual field (right hemisphere) advantage with the dot enumeration task. This study also revealed smaller N100 amplitudes for stimuli presented in left visual field (right hemisphere) than right visual field (left hemisphere) (Bruder et al., 1992). This effect was specific for depressive BD patients. In contrast, major depressive disorder patients and healthy controls did not show any FCAs in N100. Although Bruder et al. did not localize the source of this effect, it is interesting to know that lesions in right parietal regions were associated with impaired dot enumeration performance (Warrington & James, 1967), again suggesting right parietal dysfunction in BD patients.

Spatial attention is another key function of the right hemisphere. Although each hemisphere is involved in allocating attention towards the contralateral hemispace, it has been proposed that the right hemisphere allocates attention to both, the left and right hemispaces, suggesting its dominant role in spatial attention (Heilman & Valenstein, 1979; Heilman & Van Den Abell, 1980; Mesulam, 1981). A right parietal dysfunction in BD has been shown by a positron emission tomography (PET) study using a serial reaction time task, attributed to visuospatial function, in which participants are visually cued to press one of four buttons at a time (Berns, Martin, & Proper, 2002). It has been shown that responses to this task involve manifestations of shifts of visuospatial attention to likely stimulus locations (Marcus, Karatekin & Markiewicz, 2006). In Berns et al.'s study, BD patients exhibited significantly

reduced activation in the right superior parietal cortex compared with healthy controls when finger sequence changed, which might have compromised visuospatial processing. However, Berns et al. employed a bimanual RT task, rather than examining one hand at a time, and therefore it is difficult to interpret the normal hemispheric pattern during bimanual performance.

A more reliable measurement of the right hemisphere dominance in spatial attention is the visual line-bisection task (e.g., Brodie, & Pettigrew, 1996; Hausmann, 2005; Hausmann, Ergun, Gunturkun, & Yazgan, 2002; Hausmann, Corbalis, & Fabri, 2003a; Hausmann, Corbalis,& Waldie, 2003b; MacLeod & Turnbull, 1999; McCourt, Chaussee, Freeman, & Tahmahkera-Stevens, 2001; Roig & Cicero, 1994; for review see Jewell & McCourt, 2000). Participants are asked to bisect horizontal lines into two parts of equal length by marking the subjective midpoint of each line with a fine pencil. Patients with right inferior parietal lesions show a strong rightward bisection bias (e.g., Schenkenberg, Ajax, & Bradford, 1980), which is explained as the result of the left hemisphere being exclusively concerned with attention to the contralateral right hemispace. Normal controls also show a bias but tend to systematically bisect lines to the left of the objective middle, suggesting that although the right hemisphere is dominant in spatial attention and can direct attention to both sides of space, it slightly favours left hemispace (e.g., Bowers & Heilman, 1980). The stronger right hemisphere involvement in spatial attention during line bisection (LB) has been supported by neuroimaging and neurophysiological studies (Cicek, Deouell, & Knight, 2009; Fink et al., 2000; Foxe, Javitt, & McCourt, 2003; Waberski et al., 2008). The right hemisphere dominance in allocating attention is also confirmed by the fact that the leftward bias is especially pronounced when subjects use their left hand (corresponding to the right hemisphere) to bisect lines (e.g., Brodie & Pettigrew, 1996; Hausmann, 2005; Hausmann, et al., 2002, 2003a,b; MacLeod & Turnbull, 1999; McCourt et al., 2001; Roig & Cicero, 1994; for review see Jewell & McCourt, 2000). Given that the left bias still exists when the right hand is used, this suggests interhemispheric spreading activation, probably via the corpus callosum, from the left hemisphere motor areas to the dominant attention network in the right hemisphere (McCourt et al., 2001). The role of the corpus callosum in visual LB is supported by studies on patients with callosal infarction (Corballis, 1995; Kashiwagi, Kashiwagi, Nishikawa, Okuda, & Tanabe, 1990), patients with partial or complete commissurotomy (Hausmann et al., 2003a; Heilman, Bowers, & Watson, 1984) and

younger children associated with immaturity of the corpus callosum especially in the posterior subareas (i.e., splenium).

Up to now, only one recent study has investigated visuospatial attention in BD (psychotic and non-psychotic) and healthy controls by applying a visual line-bisection task (Rao, Arasappa, Gangadhar, Reddy, & Venkatasubramanian, 2010). The results revealed a leftward bias in both psychotic and non-psychotic patients but only when the right hand was used (Rao et al., 2010). This finding is surprising since a right hemisphere dysfunction in BD patients would predict a rightward bias which is similar to that of neglect patients with right hemisphere lesions. BD patients should at least show a reduced leftward bisection bias (i.e., reduced pseudoneglect) that is usually found in normal controls, especially when the left hand is used to bisect lines (Milner, Brechmann, & Pagliarini, 1992). Rao et al.'s findings, however, did not follow this prediction. For the percentage deviation score, which takes line length into account, this study found an unusually large leftward bias (68.38 %) for the left hand in healthy controls, which is different to the leftward bias (i.e., pseudoneglect) of about 1-3% typically found in healthy controls. It should also be noted that Rao et al. averaged the bisection bias across hands. This makes it rather difficult to estimate the contribution of each hemisphere and involvement of interhemispheric processes (Jewell & McCourt, 2000). Due to these limitations further examination of visual LB in BD patients seems necessary.

BD involves a hyperactivated right fronto-parietal network particularly implicated in emotion perception suggesting that right hemisphere dysfunction is attributable of emotional stimulation (e.g., Blumberg et al., 2005; Chen et al., 2010; Lee, Chen, Chen, Hsieh, & Su, 2010; Liu et al., 2012; Morris, Green, Mitchell, Sparks, Weickert & 2012; Pavuluri, Harral, Passarotti, & Sweeney, 2009; Robinson et al., 2008; Wessa et al., 2007). The visual field, DL and PET studies mentioned above, however, found a similar right (fronto) parietal dysfunction in BD using tasks with an attentional component (Berns et al., 2002; Bruder et al., 1981, 1989, 1992, 1994). Thus, other types of stimulation in BD, such as attentional salience, may also overshoot right hemisphere dysfunction. Such attentional stimulation of the right hemisphere can be attained with the visual line bisection task. Line bisection studies placing either numbers or letters at the left or right end of the line consistently find that unilateral left cues selectively increase leftward bisection bias, through activating the contralateral hemisphere (e.g., Milner et al., 1992; Olk & Harvey, 2002). Thus, cueing

procedure that amplifies the typical response-based tendency reflecting greater right hemisphere activation, suggest differential attentional salience of the two ends of the line as a driving mechanism. Based on these findings, it is hypothesised that BD patients will show larger deviations towards the right of the veridical center when bisecting lines than healthy controls, especially when using their left hand.

Method

Participants

Twenty-two patients (13 women) with BD (Age: 44.59 ± 9.97 years) were recruited from Northumberland NHS Foundation Trust and Tees, Esk and Wear Valleys NHS Foundation Trust. All individuals fulfilled the following inclusion criteria: (1) a diagnosis of BD, type I, according with the Structured Clinical Interview for DSM-IV (SCID-P; First, Gibbon, Spitzer, & Williams, 1995), (2) no current concomitant Axis I disorder, and (3) no history of medical or neurologic condition. Individuals were also excluded if they met the DSM-IV diagnosis for anxiety disorders or substance abuse within the preceding six months.BD patients were clinically stable outpatients at the time of the study. The current depressive symptoms were assessed using the 17-item Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960). The manic symptoms were assessed with the young mania rating scale (YMRS; Young, Biggs, Meyer, & Ziegler, 1978).

As a group [HAM-D = 3.05 ± 1.98 (0–7) and YMRS = 5.18 ± 4.23 (0-10)] and based upon symptom ratings (HAM-D ≤ 7, YMRS ≤ 10), BD patients were euthymic on the day of the study. Previously anxiety symptoms were present in three patients. Five patients had a history of alcohol or substance abuse. Fifteen of the BD patients were taking mood-stabilizing medications; eight patients were taking antidepressants. In addition, twelve patients were receiving atypical antipsychotic. None of the patients with BD were experiencing psychotic symptoms at the time of the assessment.

Eighteen healthy controls (Age: 41.94 ± 10.37 years; 10 women) were recruited through local announcements (e.g., local post office, community library, Durham University, etc.). Control participants were matched for age, sex, and education and had no history of any Axis I disorder and no history of affective disorder or schizophrenia in first-degree relatives.

BD patients and healthy controls were right-handed as determined by the Edinburgh Handedness Inventory (Oldfield, 1971). The asymmetry-index provided by this test is calculated as ((R-L)/(R+L)) x 100 resulting in values between -100 and +100. This range describes the continuum from extreme sinistrality to extreme dextrality. The handedness scores for the BD patients (88.99 ± 12.51) and healthy controls (87.00 ± 16.83) did not significantly differ ($t(38) = -0.43$, n.s.).

After receiving a complete description of the study, written informed consent was obtained from each participant. The study was approved by the regional ethics committee from the NHS and Durham University Ethics Advisory Committee. All participants received £20 for participating in the study.

Procedure and Materials

The line-bisection task was identical to that used in a previous study (e.g., Hausmann, 2005; Hausmann et al., 2002, 2003a,b). It was composed of 17 horizontal black lines 1 mm wide on a white sheet of paper (21 cm x 30 cm). The lines ranged from 100 to 260 mm in length in steps of 20 mm. The mean length was 183.5 mm. They were pseudorandomly positioned so that seven lines appeared in the middle of the sheet, five lines appeared near the left margin, and five lines appeared near the right margin. The lateralised lines were 13 mm away from the margin. The line lengths for the seven centered lines were 12 cm (one line), 18 cm (two lines), 22 cm (two lines), 24 cm (two lines; $M = 20$ cm) and 10 cm, 14 cm, 16 cm, 20 cm, and 26 cm ($M = 17.2$ cm) for the five left- and five right-lateralised lines, respectively. The sheet was laid in front of the participant's midline. Participants were instructed to bisect all lines into two parts of equal length by marking the subjective midpoint of each line with a fine pencil. All participants completed the task with one hand and then repeated it with the other in a balanced order. The experimenter covered each line after it was marked to ensure that the participants were not biased by their previous choices. There were no time restrictions. The deviations to the left or to the right of each marked line were carefully measured to 0.5 mm accuracy. The percentage deviation score for each line was computed as follows: [(measured left half – true half)/true half] x 100. This measure is comparable with that used in other studies (Scarisbrick, Kuslansky, & Tweedy, 1987; Shuren, Heilman, & Wertman, 1994) and takes individual line length into account. We then computed the mean score for all lines separately for each hand.

Negative values indicate a left bias, and positive values indicate a right bias. The degree of left bias was statistically compared with a deviation score of zero (true center of the line) by calculating one-sample t-tests (Bonferroni adjusted) for each group and each hand. The absolute deviation bias (in millimeters) was also calculated, indicating the overall accuracy independent of its direction. Also, number of lines bisected to the left or right, respectively, from the center was calculated for each hand. Separate scores for left bisected, and right bisected lines ranged from 0 (all lines correctly bisected) to 17 (all 17 lines were bisected to one side).

Results

Absolute line bisection bias (accuracy)

To investigate whether euthymic BD patients and healthy controls differed in accuracy, absolute deviations in visual LB were compared between both groups. Absolute biases were entered into a 2 x 3 x 2 analysis of variance (ANOVA), with hand-use (left hand, right hand) and line position (left, center, right) as within-subject factors, and group (patients, controls) as between-subjects factors. There was a significant interaction between hand and position, $F(1, 38) = 5.34$, $p < 0.05$, $\eta^2 = 0.12$, with larger absolute deviations from the veridical center when the participants used their left hand especially when bisecting lines located near the left margin. Post hoc paired *t*-tests (Bonferroni corrected), however, did not reveal significant differences between hands for either line position (all *t*s < 2.10, n.s.). More importantly, neither the main effect of group nor any interaction with group approached significance (all $F < 2.21$, n.s.), indicating that BD patients bisected lines as accurately as healthy controls across all conditions.

Directional line bisection bias (laterality)

Percentage deviation scores of both groups were subjected to a 2 x 3 x 2 ANOVA, with hand-use (left hand, right hand) and line position (left, center, right) as within-subject factors, and group (patients, controls) as between-subjects factors. As indicated by the intercept effect, there was a significant overall leftward bias, $F(1, 38) = 5.57$, $p < 0.05$, $\eta^2 = 0.12$, suggesting an right hemispheric superiority in allocating attention. The analysis also revealed a significant main effect of hand use, $F(1, 38) =$

4.27, $p< 0.05$, $\eta^2 = 0.10$, with a larger leftward bias when using the left hand compared with the right hand. The main effect of line position was also significant, $F(1, 38) = 4.19$, $p< 0.05$, $\eta^2 = 0.10$. Post hoc paired *t*-tests revealed a significant left bias for center lines ($t(39) = -3.63$, $p< 0.005$) but not for left or right lines (both $t<$ 1.89, n.s.). The interaction between hand use and group was also significant, $F(1, 38) = 6.43$, $p< 0.05$, $\eta^2 = 0.15$. Post hoc paired *t*-test revealed a significant hand use difference in healthy controls only ($t(17) = -3.17$, $p< 0.01$). There was no effect for hand use in BD patients ($t(21) = -.34$, n.s.). As shown in Figure 1, the control group revealed the well-known and significant left bias when using the left hand ($t(17) = -4.69$, $p = 0.0002$) and no bias for the right hand ($t(17) = 0.12$, n.s.). In contrast, BD patients did not exhibit a significant bias with either hand (both $t>$ -.88, n.s.). Likewise, the comparison of the left bias between groups was significant for the left ($t(21) = -2.45$, $p = 0.019$) but not for the right hand ($t(21) = .73$, n.s.). No other main effect or interaction approached significance, (all $F < 3.76$, n.s.).

Left and right displacements of both groups were subjected to a 2 x 2 x 2 ANOVA, with hand use (left hand, right hand) and line displacement (left, right) as within-subject factors, and group (patients, controls) as between-subjects factors. There was a main effect of line displacement $F(1, 38) = 15.42$, $p < 0.005$, $\eta^2 = 0.29$), with more lines bisected to the left. No other effect approached significance (all $F <$ 3.75, n.s.).

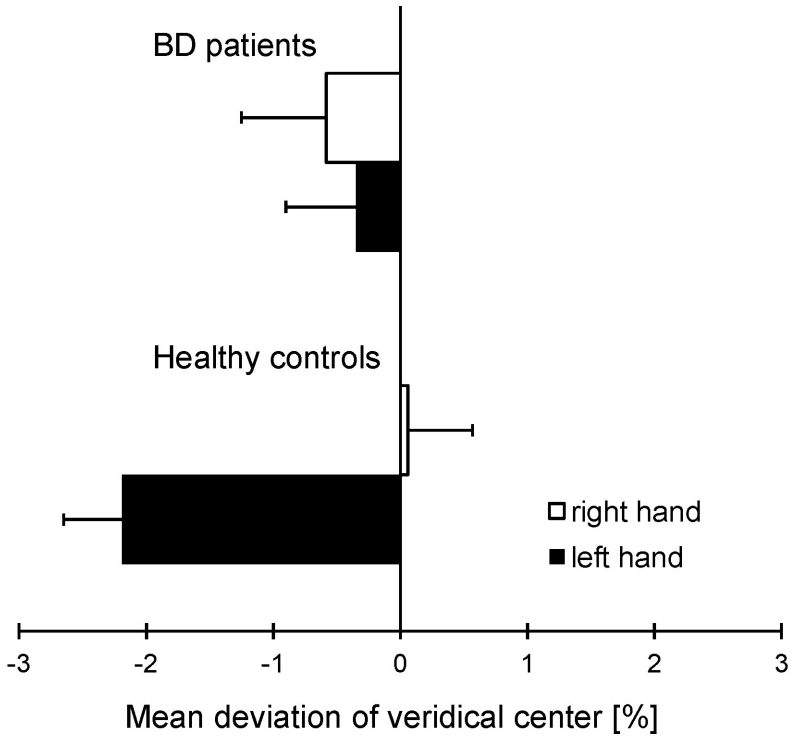

Figure 1. Mean deviations (%) and standard error means from the true center during line bisection for bipolar patients (top) and healthy control (bottom) for the left hand (black bars) and right hand (white bars). Data are collapsed across line position.

Discussion

The present study replicated the well-known overall left bias in visual LB (i.e., pseudoneglect), which has consistently been found in studies using the LB paradigm in neurologically normal individuals (McCourt & Olafson, 1997; McCourt & Jewell, 1999; Jewell & McCourt, 2000 for a review). Moreover, the present study found the typical hand-use effect in healthy controls (e.g., Brodie, & Pettigrew, 1996; Hausmann, 2005; Hausmann, et al., 2002, 2003a,b; MacLeod & Turnbull, 1999; McCourt et al., 2001; Roig & Cicero, 1994; for review see Jewell & McCourt, 2000), that is, a significantly larger left bias with the left than the right hand. The results for healthy controls are also in line with fMRI research showing that LB judgments to be associated with activation in the right superior posterior and right inferior parietal cortices (Fink et al., 2000). This activation seems to be promoted by using the left hand, which is assumed to be particularly under the control of the attention-dominant right hemisphere (Milner et al., 1992).

Although the overall left bias did not significantly differ between groups, BD patients did not show the typical leftward bias with the left hand. In fact, the bisection

bias with either hand did not significantly differ from the veridical center. It seems that BD patients placed the LB mark closer to the veridical center. The analysis of the absolute bias (regardless of its direction) suggests, however, that BD patients and healthy controls were similarly accurate in LB. The strongly reduced directional left hand LB bias in BD patients indicates a reduced FCA in spatial attention, suggesting a dysfunction of parietal areas of the right hemisphere.

To the best of our knowledge, the only available LB study on BD is the study by Rao and colleagues (2010). Among a number of limitations mentioned previously, the study failed to show the well-known pseudoneglect in healthy controls. In fact, the percentage deviation score for the left hand in healthy controls showed an unusually large left bias (68.38 %). The deviation biases in healthy controls usually ranges from 1% to 3% with respect to the length of the line (for a review see Jewell & McCourt, 2000). The left hand LB bias of 2% found in normal controls within the present study falls into this expected range. Also, the hand use difference was not examined in Rao et al.'s study. It is unlikely that methodological issues can account for these unexpected findings. The LB task used in Rao et al. and the present study overlaps considerably in various aspects. For example, the LB task used in the present study included horizontal lines presented in the middle or close to the left and right margins of the sheet. Similarly, Rao et al. (2010) also used lines presented close to the left and right margins. Also, the present study used line lengths ranging from 100-260 mm (in steps of 20 mm). Rao et al.'s study used line lengths between 70-160 mm (in steps of 10 mm).

Contrary to our prediction of a large leftward bias for both hands in BD, the present findings show a hand use difference between BD patients and healthy controls mainly driven by the reduced leftward bias in BD patients when using the left hand (corresponding to the right hemisphere). Although this finding is difficult to explain in terms of an overactivated right hemisphere in BD, it supports the assumption of right parietal dysfunction in BD patients (Berns et al., 2002; Bruder et al., 1981, 1989, 1992, 1994). The non-significant left hand bias, as found in BD patients within the present study, suggests an underactivation of the right parietal cortex (McCourt et al., 2001). In line with a number of recent studies (Kim et al., 2012; Lee et al., 2010; Liu et al., 2012) parietal regions are especially involved in the pathophysiology of BD. However, two of these magnetoencephalographic (MEG) studies also showed right parietal hyperactivity in an implicit emotional faces task in BD (Lee et al., 2010; Liu

et al., 2012). Specifically, Lee and colleagues (2010) examined BD and major depressive disorder patients using an implicit paradigm requiring participants to judge the gender (a non-emotional facial cue) of emotional faces while recording event related MEG signals. In contrast to major depressive disorder patients and healthy controls, BD patients exhibited an increased activity in the right inferior parietal gyrus (Lee et al., 2010). However, differences between the present study (using a LB task that is unrelated to emotional processing and measures spatial attention), and both MEG studies, (using arousing emotional (face) stimuli), may explain discrepancies in the direction of right fronto-parietal activation.

The present study confirms previous studies that have used the visual LB task as a valuable tool for assessing the functional brain organisation associated with the pathophysiology of different neuropsychiatric disorders (Barnett, 2006; McCourt, Foxe, Javitt, & Shpaner, 2008). For example, LB studies in children with attention-deficit hyperactivity disorder (ADHD) have consistently shown a rightward bias in spatial attention, suggesting a right hemisphere inefficiency associated with symptoms of severe impulsivity and/or hyperactivity (Manly et al., 2005; Rolfe et al., 2008; Sheppard et al., 1999; Waldie & Hausmann, 2010;). Also, the leftward bias in LB (i.e., pseudoneglect) that usually characterizes the right-hemisphere dominance for the allocation of visuospatial attention observed in neurologically normal subjects was increased in dependent personality disorder (Wang et al., 2003), and similar to the present study, significantly reduced in schizophrenia (Barnett, 2006; Mather, Merskey, Neufeld, & Russell, 1990; McCourt et al., 2008; Zivotofsky, Edelman, Fostick, Green, & Strous, 2007). Thus, these findings suggest that the visual LB is sensitive to atypical functional brain organisation across different neuropsychiatric disorders.

Adding to the LB literature in neuropsychiatric disorders, the present study found a reduced leftward bisection bias in euthymic BD patients suggesting a reduced dominance of the right hemisphere in spatial attention, perhaps as a result of functional alterations within the right parietal cortex. In contrast to manic or depressive BD episodes, euthymic BD patients experience a state that is close to 'normal' mood. Therefore, the present findings in BD euthymia suggest an atypical brain organisation in spatial attention, perhaps as a result of functional alterations within the right parietal cortex, regardless of mood symptoms.

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Chapter 7

General discussion

The present thesis aimed to investigate the functional brain organisation of emotion processing. To assess this question FCAs underlying the perception of emotions was studied in healthy controls. In addition, FCAs were investigated in subclinical affective subjects and euthymic BD patients as an experimental model for studying (a) emotional processing and (b) a BD continuum. On the one hand, the processing of emotions in healthy individuals revealed a predominant right hemisphere involvement in the perception of negative (only) emotions. On the other hand, behavioural and neuroimaging approaches in BD patients and/or subclinical affective subjects, revealed an atypical functional brain organisation in both cases, supporting a broader concept of bipolarity.

7.1. Right hemisphere involvement in the experience of emotion

Chapter 2 describes a study reviewing previous visual half-field studies of FCAs in emotion perception and re-evaluates empirical evidence with respect to the Right Hemisphere Hypothesis, the Valence-Specific Hypothesis and Approach/Withdrawal model of emotion perception. To evaluate the explanatory power of these three competing hypotheses it was important to directly compare them as well as analysing FCAs for the six basic emotions. FCAs for the perception of specific facial emotions did not account for any of the three models without restrictions. Similarly, all the patient studies (Chapter 4 to 6) suggested a lack of support for the asymmetry models, showing atypical FCAs in BD euthymia. These findings imply relative hemisphere differences regardless of valenced emotional experience. Chapter 2 showed a robust right hemisphere advantage for negative emotions. This finding is in line with a recent meta-analysis on unilateral damage studies assessing facial emotion perception (Abbott, Cumming, Fidler, & Lindell, 2012). Although left and right damage patients were associated with a deficit in perceiving emotions in general, right hemisphere damage patients exhibited a larger tendency for impaired perception of negative relative to positive emotions. However, this review did not evaluate hemispheric

asymmetries in terms of specific emotions. The review on Chapter 2 revealed that no final conclusions could be drawn given that FCAs in terms of individual emotions have been only assessed by studies using a small number of emotions. This gap has been addressed by the experiment of Chapter 2 that assessed FCAs for the perception of the six basic emotions revealing a right hemisphere involvement for fear, sad and angry expressions.

This finding is in line with previous neuroimaging studies showing a right fronto-temporal involvement in the perception of fearful, sad, and angry facial expressions (e.g., Blair et al, 1999; Morris et al., 1998a). Also, this particular subset of emotions seems to prompt sympathetic activation as revealed by findings of marked increases in heart rate for the AFS subset in contrast with other more positively valenced emotions (Ekman, Levenson, & Friesen, 1983; Levenson, 1992). One may claim that perception of the AFS subset triggers emotional responses via bodily states (i.e., heart rate) to generate own emotional states. This can occur via a "body loop" in which a "somatic marker" is conveyed to somatosensory cortices (Benchara Damasio & Damasio, 2000; Damasio, 1994). Thus the study in Chapter 2 may be explained in terms of a right hemisphere mechanism underlying emotional experience, induced by the perception of the AFS subset. The right hemisphere involvement in emotional experience has been further supported by the patient studies presented here that showed a consistent right hemisphere dysfunction. Thus induced emotional experience may have arisen from intense arousal and salient distress underlying the perception of the AFS subset. This interpretation is compatible with a study examining the effects of facial emotion perception on both cardiac responses and brain activation (Critchley et al., 2005). Critchley et al. (2005) stressed a basic autonomic principle differentiating between emotions with greater parasympathetic-activity and those involving a sympathetic dominance. Whereas processing of happy and disgust faces attenuated heart rate, sad and angry faces accelerated heart response. In addition, emotional effects involved brain activity in the anterior cingulate cortex, amygdala, and temporal lobe. Although this particular study did not assessed fear expressions limiting support for the AFS model, notably two previous studies confirmed a heart rate acceleration for anger, fear and sad relative to other emotions (Ekman et al., 1983; Levenson, 1992). In sum, valenced asymmetry models failed to predict the findings of both, healthy control and patient studies; however these studies seemed to converge on a right hemisphere involvement in emotional experience.

7.2.1 Thinking profile in bipolar disorder euthymia

As previously described, the study on healthy controls from Chapter 2 revealed a specific right hemisphere role in the processing of an AFS subset that may have instantiated emotional experience. Consistent with this interpretation the studies in BD patients and healthy individuals with hypomanic traits found a right hemisphere dysfunction. These results showed atypical emotional response involving a reduced right hemisphere advantage in emotional prosody. Overall these findings support the assumption that the right hemisphere is putatively involved in the experience of emotion.

It should be noted, however, that the studies from Chapters 4 and 6 still revealed right hemisphere involvement in the absence of emotional stimulation. These findings suggest a common atypical brain organisation underlying behavioural patterns across tasks. BD behavioural performance may have been subserved by cognitive style, which consists on individual's preferred and habitual approach to organise, represent, and process information (Streufert & Nogami, 1989). In fact several influential models in bipolar and affective disorders have explained brain organisation in terms of cognitive styles. For instance, the "interhemispheric sticky switching" model of Pettigrew and Miller claims that mood shifts result in distinct cognitive styles. This model predicts that left hemisphere lateralisation leads to manic-related tendencies of elation and confidence, and right hemisphere lateralisation relates to depressive dispositions such as apprehension and low self-esteem. The logic on complementary cognitive styles of this theory is based on observations of right- compared to left-sided lesion patients exhibiting anosognosia (denial of disease) (McGlynn & Schacter, 1989), and the assumption that left hemisphere's cognitive style is goal-directed with a coherent plan of action. Thus, goal directed behaviour resulting from a manic cognitive style and inhibited responses resulting from a depressive cognitive style, may contribute to monitoring and guiding behaviour in BD. This is in line with a recent reformulation of the behavioural activation system (Urosevic, Abramson, Harmon-Jones, & Alloy, 2008), suggesting that two complementary appraisal processes mediate BD behaviour. On the one hand, efficacy appraisal refers to beliefs in one's ability to bring about a desired outcome. On the other hand, relevance appraisal involves expectancy of success. Thus, increased strength in the efficacy or relevance appraisals is likely to induce a similar increase in the behavioural activation

system leading to manic symptoms. A decrease in the magnitude/strength of these two processes, in turn, might be related to the expression of hypomanic/depressive symptoms.

At the level of the functional brain organisation, left hemisphere lateralisation is predicted to increase in mania and decrease in depression. Thus according with a dysrregulated behavioural activation system in BD, deviations in functional brain organisation associated with mood and cognitive styles are capable of influencing behaviour (Urosevic et al., 2008). A cognitive style associated with mania guides behaviour in a goal directed manner, resulting in patterns of behavioural over-activity. This is consistent with clinical observations that manic symptoms involve marked increase in productivity, decreased need for sleep, increased energy, increased self-esteem and increased confidence (Benazzi, 2007). In contrast, a depressive cognitive style has been characterized by decreased motivational drive, reflected on pervasive clinical consequences such as unmitigated depressive inhibition, and even failure to look after own physical needs. A BD cognitive style is also in line with Beck's prominent cognitive theory of depression (Beck, 1967). While extreme negative beliefs are reported in BD depression (Scott & Pope, 2003; for a review, see Mansell & Scott, 2006), excessively positive and self-relevant interpretations have been related to manic symptoms (Healy & Williams, 1989; Jones, 2001; Scott & Pope, 2003). In sum, appraisal of goal importance and success expectancy are exacerbated in mania and inhibited in depression. Linke et al. have ventured a putative mechanism arguing that affective episodes act as specific learning experiences facilitating beliefs about one's ability to show a behaviour (failure versus success) and beliefs about one's ability to control outcome (reward versus punishment) (Linke, Sonnekes, & Wessa, 2011).

It should be noted that all these models linking atypical brain organisation in BD with behavioural patterns only explain symptomatic phases. However, if atypical organisation of the brain is intrinsically related to BD, behavioural alterations should also affect euthymic states, as shown by the present studies. In fact, the results from Chapter 4 supported intrinsic brain mechanism in euthymic BD, involving atypical right amygdala connectivity during rest. Moreover, in the behavioural patient studies presented here, a common atypical functional brain organisation in BD euthymia underlies behavioural responses in different processes. Chapter 6 describes a study that suggested a reduced right hemisphere specialisation in spatial attention in

euthymic BD patients. In addition, the DL studies from Chapter 3 and 5 showed a reduced right hemisphere advantage in emotional processing in euthymic BD patients similar to that in healthy individuals with hypomanic related traits. These converging FCAs across different tasks insinuate that the models above on acute mood phases can be extended to a more inherent functional brain organisation of BD involving a thinking profile also in euthymic BD patients.

In support of this hypothesis, several studies have shown dysfunctional appraisals in euthymic BD patients (Alatiq, Crane, Williams, & Goodwin, 2010; Dodd, Mansell, Sadhnani, Morrison, & Tai, 2011; Mansell, 2006; Mansell & Jones, 2006). Most of these studies have used a measure of positive and negative appraisals that is, the hypomanic attitudes and positive prediction inventory consisting of statements about how participants feel when they are in a certain mood. Positive appraisals involve excessively positive interpretation of high mood, such as signifying imminent success and prompting ascent behaviours. Conversely, negative appraisals involve interpreting mood in a self-critical way leading to descent behaviours, such as withdrawing from social situations. BD remitted patients have been associated with higher positive and negative appraisals compared to MDD patients and healthy controls (Alatiq et al., 2010). In particular, remitted BD patients were associated with catastrophic interpretations of low mood and dysfunctional positive appraisal of elevated mood. Also, euthymic BD patients have been linked with positive self-dispositional appraisals of hypomanic experiences, suggesting that trait-like beliefs associated with mania are maintained during euthymia (Mansell, 2006; Mansell & Jones, 2006). One study assessed conviction in a range of positive and negative appraisals of mood state in a nonclinical sample with either history of hypomania or depression (Dodd et al., 2011). Whereas a history of hypomania was associated with more positive and less negative appraisals of high mood, a history of depression was associated with more negative appraisals and less positive appraisals of low mood. Overall these studies suggest an euthymic thinking profile involving a tendency to hold extreme appraisals (positive and negative) and influencing behavioural patterns regardless of mood phases. These findings extend Pettigrew's prediction of atypical brain organisation in symptomatic BD phases by showing a specific thinking style related to atypical functional brain organisation also in BD euthymia.

7.2.2 Right hemisphere networks in bipolar disorder euthymia

As previously noted, the results of all patient studies showed atypical functional brain organisation in BD indicating a right hemisphere dysfunction. The right hemisphere involvement in BD has particularly implicated a fronto-temporal network underlying the processing of emotions. This was found by studies presented by Chapters 3 and 5, showing reduced right hemisphere advantage for prosody in euthymic BD patients and individuals with hypomanic related traits. These findings are entirely consistent with a study assessing whole brain fractional anisotropy, a measure of the structural integrity of brain white matter, in depressive BD patients (Versace et al., 2010). Findings revealed abnormally reduced right uscinate fasciculus, a major fiber tract connecting fronto-temporal regions, in BD patients compared to healthy controls, possibly disrupting processing and regulation of emotions.

A right fronto-temporal involvement in emotional processing, has been suggested by several neurological and lesion studies (Anderson, Spencer, Fulbright, & Phelps, 2000; Mendez et al., 2006; Perry et al., 2001; Rankin, Kramer, Mychack, & Miller, 2003; Rosen et al., 2002; Tranel, Bechara, & Denburg, 2002). Impairments in emotional processing in fronto-temporal dementia are found in patients affected by right compared to left temporal atrophy (Mendez et al., 2006; Perry et al., 2001; Rankin et al., 2003; Rosen et al., 2002). For example, findings from a case study revealed that a predominantly right atrophy in individuals with fronto-temporal dementia were significantly more impaired in facial and prosodic recognition of emotions than those exhibiting predominantly left atrophy (Perry et al., 2001). In contrast, patients with left temporal atrophy were particularly more impaired in semantic tasks than patients with right temporal atrophy. This last finding of left hemisphere involvement in language nicely fits the DL findings showing a preserved left hemisphere advantage in linguistic processing in BD, suggestive of a selective right hemisphere dysfunction. Further support for the right fronto-temporal role in emotion has been shown by a study investigating temporal variant of fronto-temporal dementia in facial emotion comprehension using naming, matching and selection emotional tasks (Rosen et al., 2002). Atrophy in the right amygdala and right OFC only, significantly correlated with the processing of angry, fearful, and sad facial expressions. Moreover, a clinical study on cases of frontal lobe removal due to epilepsy showed impaired recognition of sad and fearful facial expressions in the right

temporal removal group compared to the left temporal removal group (Anderson et al., 2000). Given that emotion perception involves an emotional response, as suggested by theories of embodiment of emotion (Niedenthal, 2007; for further discussion see general introduction), the right fronto-temporal network may also be engaged in the experience of emotion. Supporting this idea, Mendez et al. (2006) showed that patients with fronto-temporal dementia showing right temporal hypo-perfusion also exhibited symptoms of dysthymia. Compatible findings come from a study showing disturbances in emotional experience in patients with unilateral ventromedial prefrontal lesions (Tranel et al., 2002). Whereas right-sided lesion patients were associated with hampered emotional experience and poor modulation of emotion, as measured by the Iowa Scales, left sided-lesion patients did not exhibit such symptoms (Tranel et al., 2002). Thus, the right ventromedial prefrontal region seems critically involved in emotional experience relative to a minor role of the same area in the left hemisphere. Given the evidence showing a role of the right fronto-temporal network in perception and experience of emotion, the functioning of this network may be especially compromised in BD resulting in a reduced right hemisphere advantage for emotional processing as found in studies of Chapters 3 and 5.

Although all studies in BD and hypomanic related traits converged on the finding of a right hemisphere dysfunction, studies still differed in the specific underlying neural networks. The study described by Chapter 6, testing euthymic BD patients, suggested a right fronto-parietal involvement in BD in a visual line bisection task. These findings suggested a reduced right hemisphere specialisation in visuospatial attention in BD. This particular finding also suggested a hypoactivation in the right frontal parietal network as indicated by the absence of a bisection bias. However, this is in particular contrast with a right hemisphere hyperactivation in BD as suggested by all the other studies. It should be noted, however, that the line bisection study was the only task investigating a psychological process which was not related to emotions. Therefore, emotion dysregulation in BD seems to involve an over-stimulation of emotional networks (i.e., right fronto-temporal, right amygdala) which thereby incidentally may deactivate networks underlying non-emotional processes. This is in line with the study in Chapter 6 suggesting right fronto-parietal hypoactivation in BD during a spatial attention task. This idea is further supported by an fMRI study using a non-emotional n-back task measuring working memory (Townsend, Bookheimer,

Foland-Ross, Sugar, & Altshuler, 2010). Euthymic, depressed and manic BD patients showed reduced right dorsolateral prefrontal activation compared to healthy controls.

Consistent with the right fronto-parietal dysfunction, a right parietal region in BD patients showed atypical connectivity with the right amygdala in the resting state study (Chapter 4). However, whereas all the BD studies supported a right fronto-posterior network, the resting state study did not implicate right frontal regions. However the resting state study examined intrinsic mechanisms, which may not require right fronto-posterior involvement as in the task related processes investigated by all the other studies. Specifically, this study showed atypical right somatosensory influence to the right amygdala in BD, probably intensifying internal emotional states and disrupting emotion regulation.

Given that the amygdala has been consistently implicated in emotional deficits in BD (e.g., Altshuler et al., 2005; Bermpohl et al., 2009; Foland et al., 2008; for a meta-analysis see Chen, Suckling, Lennox, Ooi, & Bullmore, 2011), these findings are suggestive of an atypical resting state amygdala mechanism associated with deficits in emotion regulation. In fact, it has been recently argued that BD implicates an unsuccessful regulatory system for decreasing (or increasing) the levels of affect (Gruber, Harvey & Gross, 2012a). This claim is grounded on evidence showing that BD is associated with greater magnitude of emotional reactivity (Gruber, Eidelman, Johnson, Smith, & Harvey 2011b; Gruber, Harvey, & Purcell, 2011a; Gruber, Johnson, Oveis, & Keltner, 2008; Gruber, Purcell, Perna, & Mikels, 2012b; Gruber et al., 2012a; Forbes et al., 2005; M'Bailara et al., 2009), prolonged duration to engage in feelings (Forbes et al., 2005; Gruber et al., 2011b) and thoughts and deficits in emotion maintenance (Gruber et al., 2012b). A well known adaptive strategy for emotion regulation is *cognitive reappraisal* (Gross, 1998), involving recruitment of cognitive resources to interpret the context of salient emotional stimuli to modulate their emotional response. In contrast, a maladaptive strategy for regulating emotions is *expressive suppression* (Gross, 1998; Gross & Levenson, 1997) consisting in the inhibition of emotion-expressive behaviour. A recent study examined emotional regulation strategies in euthymic BD patients as well as success and effort in regulating emotions (Gruber et al., 2012a). As predicted, euthymic BD patients compared to healthy controls viewing emotional films evidenced higher involvement in maladaptive (i.e., suppression) emotion regulation, and greater efforts for regulating irrelevant stimuli (i.e., neutral films). Disruption of these mechanisms

suggested that BD is associated with indiscriminated and ineffective attempts for regulating emotions. Another emotion regulation strategy, *rumination*, involves repetitive thoughts and feelings on one's affective states (Gross, 1998). As shown by Gruber et al. (2011b), remitted BD patients exhibited greater rumination associated with amplifying positive and negative emotions, suggesting prolonged engagement in emotional states. *Maintenance* of emotions (Gross, 1998) is another mechanism influencing emotion regulation, consisting in a series of processes sustaining the subjective experience of emotion. Negative emotion maintenance was found in BD patients compared to healthy controls, suggesting a selective deficit in negative emotion maintenance. Unsuccessful emotion regulation in BD was also associated with emotion hyperreactivity (Gruber et al., 2011a; M'Bailara et al., 2009) during both, emotional and neutral films. Taken together these findings indicate that BD is associated with several deficits in emotion regulation, presumably involving emotional brain networks.

A good candidate, is the right fronto-temporal network involved in emotional processing (e.g., Anderson et al., 2000; Mendez et al., 2006; Perry et al., 2001; Rankin et al., 2003; Rosen et al., 2002; Tranel et al., 2002) and, as shown in Chapters 3 and 5, is particularly associated with impaired emotion perception in BD. Several of these deficits (i.e., emotion hyperreactivity) explicitly involve emotion perception, which is one of the specific functions subserved by the right fronto-temporal network (e.g., Anderson et al., 2000; Perry et al., 2001; Rankin et al., 2003; Rosen et al., 2002; Tranel et al., 2002). However, processes such as emotion maintenance and rumination take place regardless of emotional stimulation (Gross, 1998). Consequently, deficits in these processes may either involve: (a) that BD is likely to expend more efforts regulating as a result of coping with chronically heightened emotion intensity or (b) BD exhibit lower threshold for emotional reactions that are more difficult to manage, and consequently lead to less successful regulation in such elevated levels of affect. In either case, heightened levels of emotion or lower threshold for emotional reactions, BD should involve internal emotional states that are likely to implicate intrinsic amygdala mechanisms. This interpretation would be in line with the results of Chapter 5 suggesting atypical connectivity in default amygdala mechanisms of the right hemisphere in euthymic BD patients.

Under normal functioning, the assumption of internal emotional states linked to the right amygdala network, are supported by findings showing that the right hemisphere

(Adolphs, 2002; Najt, Bayer, & Hausmann, 2012) and right amygdala (Abercrombie et al., 1998; Angrilli et al., 1996; Cahill et al 1996; Rosen et al., 2002; Schaefer et al., 2000) are preferentially involved in emotional processing. For example, increased activity in the right amygdala predicted recall of negative emotional films as shown by a positron emission tomography study (Cahill et al 1996). Other studies suggested that the right amygdala is associated with mechanisms of unconscious neural response to emotional stimuli (Costafreda, Brammer, David, & Fu, 2008; Hung et al., 2010; Luo et al., 2009; Morris, Ohman, & Dolan, 1998b, 1999; Williams et al., 2006). For example, a recent meta-analysis revealed that whereas linguistic processing was associated with left amygdala lateralisation, processing of masked facial expressions of emotion in general involved right amygdala lateralisation (Costafreda et al., 2008). Also, a magnetoencephalographic investigation examining the association of awareness and emotional content of the stimuli, found that subliminal emotional stimuli were associated with increases in gamma event related synchronisation in the right amygdala (Luo et al., 2009). These findings suggest that emotionally laden or masked stimuli can be detected without awareness by complex mechanisms, enabled by a right amygdala network. However, it remains unclear how such a challenging computation can be accomplished by the right amygdala mechanisms.

The amygdala also modulates autonomic functions which may be important for the processing of emotions (LeDoux, 2000). In an attempt to address this issue, Gläscher and Adolphs (2003) tested patients with left, right and bilateral amygdala damage during emotional processing and skin conductance response. Presentation of masked emotional pictures revealed overall impairment in skin conductance response, especially in right amygdala damage patients, also present in bilateral but not in left damage patients. These findings were also confirmed by a case study of right amygdala damage associated with impaired skin conductance during emotional processing (Angrilli et al., 1996). These studies suggest that the right amygdala mediates automatic mechanisms associated with bodily sensations (e.g., skin conductance response) that may serve to sustain emotion processing. Thus, the findings of atypical right amygdala network in BD, may not only engage in emotional processing, but also relate to visceral-body sensations that facilitate the experience of emotions. Despite differences, patient studies presented here suggest a common functional brain organisation in BD particularly involving a right fronto-temporal network associated with emotional experience.

7.2.3. *A bipolar disorder continuum relying on euthymia*

As previously noted, the right hemisphere dysfunction consistently identified by all the patient studies presented here (Chapters 4 to 6) was paralleled by findings in healthy participants with high hypomanic related traits (Chapter 3). These findings coupled with previous evidence of atypical FCAs in symptomatic BD patients (e.g., Allen, Iacono, Depue, & Arbisi, 1993; Altshuler et al., 2008; Foland et al., 2008; Harmon-Jones et al. 2002, 2008; Jogia, Haldane, Cobb, Kumari, & Frangou, 2008; Kano, Nakamura, Matsuoka, Iida, & Nakajima, 1992; Liu et al., 2012; Nusslock et al., 2012; Strakowski et al., 2011) are suggestive of a shared functional brain organisation across a BD continuum.

In line with this assumption, a bipolarity continuum has been previously formulated in the "bipolar spectrum" by Akiskal et al.'s (1995), and the personality traits of "ups & downs" by Angst (2002, 2003). Akiskal et al. (1995) conceptualise BD as a continuum between BD type I (involving mania) and type II (hypomania) from the official nomenclature (DSM I-V) at a higher end, and 'softer bipolar' conditions of BD type III and IV at a lower end. According to Akiskal's "bipolar spectrum", BD type III describes a typology of BD patient with depressive symptomatology, which incurs in milder and shorter hypomania usually arising from pharmacotherapy with antidepressants. There are also individuals with subthreshold hypomanic traits which constitute the stable temperamental baseline of the BD type IV. These individuals are usually male (Akiskal, 2007; Cassano, Akiskal, Perugi, Musetti, & Savino, 1992; Depue et al., 1981; Eckblad, & Chapman, 1986) and exhibit depressive episodes of late onset (>50 years; Akiskal, 1996; Akiskal & Mallya, 1987). Complementing this BD spectrum conceptualisation, results of Chapter 3 showed sex- and trait-dependent functional brain organisation. Specifically, healthy males, but not females, with high hypomanic related traits revealed a reduced right hemisphere advantage for emotional prosody. This finding is in line with Akiskal's idea, as the male subgroup in Chapter 3 falls into the category of BD type IV which has been shown to be more frequent among men than women (Akiskal, 2007; Cassano et al., 1992). Also, in line with differences between clinical versus subclinical bipolar presentations, sex differences associated with atypical FCAs were selectively present in individuals with high hypomanic traits (Chapter 3) as compared to the patient

studies (Chapters 4 to 6). Similarly, whereas BD type IV is more frequently found in men than in women (Akiskal, 2007; Cassano et al., 1992; Depue et al., 1981; Eckblad, & Chapman, 1986) suggesting higher vulnerability, the classical BD classifications (BD type I and II) evenly affects both sexes (Diflorio & Jones, 2010).

It should be noted that, although these models argue for a bipolarity continuum, they rely on a discontinued spectrum fragmented into diagnostic categories. Moreover, these models are clinically oriented and based on BD symptoms without the inclusion of euthymia. In contrast to these symptom-oriented views, more stable and inherent aspects of BD can be tapped by a BD continuum anchored at euthymic states. Thus euthymia, as an intermediate state, is critical for the investigation of a continuum in BD as being phenomenologically similar to usual mood, but also characterised by BD aspects that persists throughout mood episodes. Such BD continuum laying in euthymia is consistent with deviations in the organisation of personality, similarly involving high neuroticism in euthymic (Bagby et al., 1996, 1997; Barnett et al., 2011; Jabben et al., 2012; Nowakowska, Strong, Santosa, Wang, Ketter, 2005; Solomon et al., 1996; Srivastava, & Ketter, 2010) and symptomatic BD patients (Barnett et al., 2011; Jabben et al., 2012; Lozano & Johnson, 2001).

The challenge then is to explain why neuroticism is persistently linked to BD throughout mood states. According to a recent study assessing emotion regulation in individuals with high and low neuroticism, this link seems to be rooted on emotion regulation (Di Simplicio et al., 2012). The study showed successful emotion regulation in individuals with low neuroticism, and difficulty in regulating emotions in individuals with high neuroticism. Thus the elevated neuroticism observed in BD across mood states implies a trait related-dysfunction in emotion regulation, which is consistent with previous findings (Gruber et al., 2008, 2011a, 2011b, 2012a, 2012b; Forbes et al., 2005; M'Bailara et al., 2009). However, if high neuroticism underlies a continuum phenomenon in BD, one would expect to find even more pervasive patterns in full-blown BD. Consistent with this assumption, euthymic BD patients (Lozano & Johnson, 2001) and nonclinical individuals with a depressive tendency (Murray, Goldstone, & Cunningham, 2007) showed elevated patterns of neuroticism, but not as high as those observed in symptomatic BD patients.

Similarly, at the level of the functional brain organisation, atypical FCAs may gradually increase across the euthymic-acute BD continuum. In line with this prediction, atypical FCAs in manic and depressive BD patients have been shown by

studies using a DL click detection task assessing selective attention (Bruder, Sutton, Berger-Gross, Quitkin, & Davies, 1981; Yozawitz et al., 1979). Manic and depressive BD patients, in contrast to healthy controls, revealed an atypical REA for click detection (Bruder et al., 1981; Yozawitz et al., 1979), suggesting atypical left hemisphere superiority in selective attention. These findings suggest more pronounced atypical asymmetries in acute BD compared to healthy controls. However, in contrast with the results of Chapter 3 in individuals with hypomanic traits and Chapter 5 in euthymic BD patients (Bruder et al., 1981; Yozawitz et al., 1979), only symptomatic BD patients show a subdominant left hemisphere involvement, which may reflect a shift in FCAs in symptomatic but not euthymic or subclinical BD.

However, since extreme expressions of BD typically involve psychotic proportions, a BD dimensional view should also explain this more severe symptomatology. It has been suggested that cognitive and emotional processes underlying neuroticism traditionally associated with affective disorders (Bagby et al., 1996, 1997; Barnett et al., 2011; Jabben et al., 2012; Nowakowska et al., 2005; Solomon et al., 1996; Srivastava, & Ketter, 2010) also contribute to the liability for psychosis (Krabbendam, & van Os, 2005). This hypothesis has been substantiated by three large-scale population based prospective studies assessing the role of neuroticism as a risk factor for the development of psychosis in individuals with no lifetime history of psychosis (Goodwin, Fergusson, Horwood, & Lawton, 2003; Krabbendam et al., 2002; van Os & Jones, 2001). For example, Goodwin et al. (2003) found that high neuroticism in mid adolescence was associated with later psychotic symptoms, raising the possibility that the levels of neuroticism may be a precursor of subsequent psychotic symptoms in early adulthood. This conclusion was similarly supported by another longitudinal study investigating the linkages between neuroticism at age 16 and increased risk of schizophrenia in adulthood (van Os & Jones, 2001).

Although psychotic symptoms can be subsumed under the BD continuum, the question arises as to whether the link between neuroticism and psychotic disorders including schizophrenia suggest a broader dimension ranging from BD to schizophrenia. In fact, associations between schizophrenia and emotional processes argue in favour of such expanded continuum. In fact, affective dysregulation has been proposed as a triggering mechanism including a miss-interpretation of experiences

that in turn increases the risk for positive psychotic experiences (Holt et al., 2006). For example, Holt et al. (2006) found that patients with a diagnosis of schizophrenia who had delusions were more likely to assign (negative) affective meanings to neutral stimuli compared with those without delusional ideation. On the basis of these findings it was proposed that formation and maintenance of delusions arise from a tendency to misattribute affective meaning to neutral information. Similarly, other studies have shown indications of emotion dysregulation in schizophrenia, therefore suggesting an extended bipolarity continuum to schizophrenia (Henry, Rendell, Green, McDonald, & O'Donnell, 2008; Henry et al., 2007; van der Meer, van T Wout, & Aleman, 2009). Schizophrenia seems to even compromise a specific mechanism of emotion regulation. Individuals with schizophrenia and current auditory hallucinations showed increased use of expressive suppression, an ineffective strategy for reducing the experience of unwanted emotions (Gross, 2002; Gross & John, 2003), which was positively correlated with the severity of hallucinatory experience (Badcock, Paulik, & Maybery, 2011).

Complementing the findings above, patients with BD and schizophrenia have shown similar deficits in executive functioning (Malhi et al., 2007; Martinez-Aran et al., 2008; Mur, Portella, Martinez-Aran, Pifarre, & Vieta, 2007; Zubieta, Huguelet, O'Neil, & Giordani, 2001). Notably, there have been indications of substantial overlap of executive impairments between BD and schizophrenic patients (Krabbendam, Arts, van Os, & Aleman, 2005; Tabares Seisdedos et al., 2003; Zalla et al., 2004). Among the different executive functions, impairments of response inhibition have been found in both disorders. Pathological impulsivity is a prominent feature in BD, (Peluso et al., 2007; Swann, Anderson, Dougherty, & Moeller, 2001; Swann, Dougherty, Pazzaglia, Pham, & Moeller 2004; Swann, Lijffijt, Lane, Steinberg, & Moeller, 2009; Swann, Pazzaglia, Nicholls, Dougherty, & Moeller, 2003; Swann, et al., 2005, 2011) which has been related to deficiencies in the regulation of response inhibition (Bora, Yucel, & Pantelis, 2009; Robinson et al., 2006; Swann et al., 2009). Similarly, numerous studies indicate severe executive impairments in patients with schizophrenia (Kolb & Whishaw, 1983; Liddle & Morris, 1991; Morris, Rushe, Woodruff, & Murray, 1995). For example, intentional inhibition of non-emotional stimuli was found to be abnormal in individuals with schizophrenia and significantly correlated with the severity of auditory hallucinations (Waters, Badcock, Maybery, & Michie, 2003). Also, failure to inhibit a prepotent response during an interference task

similarly affected euthymic BD and schizophrenic patients (Zalla et al., 2004). However, whereas euthymic BD patients were only affected on this specific function, schizophrenic patients performed poorly on a wide range of other executive measures. Overall, both disorders are associated with impaired executive functioning, particularly affecting response inhibition. Altogether, impairments in executive function and emotion regulation suggest joint participation in the continuum ranging from BD euthymia to schizophrenia. This has been supported by findings that executive functions, and response inhibition in particular, play a prominent role in emotion regulation by enabling suppression of the more automatic aspects of emotional responding (Gyurak, Goodkind, Kramer, Miller, & Levenson, 2012). For example, higher executive functioning has been related to greater reduction in visible signs of emotional behaviour in response to a loud noise (Gyurak et al., 2009).

The BD-psychosis continuum may also be reflected by the way the brain is organised. An integration of the psychotic end in the BD continuum has been supported by findings of pervasive atypical FCAs in psychotic patients (e.g., Collison, Mackay, Jiaqing, James, & Crow, 2009; Green, Hugdahl, & Mitchell, 1994; Hugdahl et al., 2008a, 2008b; McGuire, Shah, & Murray, 1993; Sommer & Diederen, 2009; Sommer et al., 2008, 2010). Although these patterns resemble the shifted atypical FCAs in symptomatic BD patients, they are in clear contrast to the more moderate pattern found in euthymic BD patients. Specifically, an imbalance in right hemisphere activation has been linked to non-self origin, negative emotional content or lack of conscious control of auditory-verbal hallucinations (Sommer & Diederen, 2009). In contrast, hypotheses regarding language lateralisation in psychosis have been divided between left (Hugdahl et al., 2008a, 2008b) and right (Sommer et al., 2008, 2010) lateralisation. This has been reflected in conflicting reports of increased activation of both, the right (Sommer & Diederen, 2009; Sommer et al., 2008) and the left hemispheres (McGuire et al., 1993). In a conciliatory interpretation, Gainotti (1972) has argued that intrusive negative thoughts and emotions, termed as “catastrophic thoughts”, could be elicited from the right hemisphere after weakening of left hemisphere inhibitory functions, due to left hemisphere pathology. Thus, the originating mechanism may still be in the left hemisphere, while the secondary effect of this is observed in altered right hemisphere activation. In support of this claim, DL studies have shown a reduced REA in response to spoken syllables (Collison et al., 2009; Green et al., 1994). The reduced REA for detecting spoken syllables in

schizophrenia have even been linked with reduced volume in the left temporal lobe. Moreover, hallucinating patients showed improvements after transcranial magnetic stimulation applied over the left temporoparietal region compared to sham transcranial magnetic stimulation (Hoffman et al., 2007).

Altered pattern of FCAs in psychosis appear to overlap with those observed in symptomatic BD patients. However, a marked differentiation is observed with respect to euthymic BD patients associated with reduced but not shifted FCAs. Altogether, these findings suggest a BD continuum lying on euthymia as an intermediate link between normal and severely disrupted patterns of neuroticism, FCAs, and executive functioning.

7.3. Future directions

The studies described in the present thesis underscore atypical functional brain organisation in BD euthymia, putatively linked to defective emotional processes, to intrinsic mechanisms sustaining internal emotional states, to psychological processes that are unrelated to emotion, and presumably to associated emotion dysregulation. All together the finding of atypical FCAs in euthymic BD patients and healthy individuals with hypomanic traits strongly suggest a bipolar continuum ranging from nonclinical hypomanic signs to clinically diagnosed BD. However, this assumption is based on the results in BD euthymia as an intermediate state and indirect comparisons with previous studies on symptomatic BD patients. Further confirmation of this model would require more direct comparisons between nonclinical individuals, euthymic BD patients and symptomatic BD patients. One critical issue is whether atypical brain asymmetries across mood reflect the transition along a continuum from nonclinical to full-blown BD. Ideally, this question could be addressed with a longitudinal approach assessing FCAs in individuals at risk for BD and re-assessing those developing the disorder at euthymic and symptomatic phases. As in the study of Chapter 2, FCAs in emotion perception should be assessed by reliable laterality tasks (i.e., DL or VHF tasks). In particular, the prosody DL task has proved sensitivity to detect atypical FCAs in both hypomanic traits and euthymic BD patients. Therefore, based upon the data of Chapter 5, a power analysis was carried out to calculate the minimum total number of participants that is necessary to obtain significant results for future studies. With an assumed power (1 – beta) = 0.9 and a level of significance (alpha = 0.05), the

minimum total sample size is n = 24 (computed with G*Power: Erdfelder, Faul, & Buchner, 1996). Thus considering the small sample size the results obtained in Chapter 5, (but also in Chapter 3) are very encouraging and helpful in setting priorities for future studies. To further characterise the brain organisation across a BD continuum, future studies may also benefit from implementing morphometric approaches assessing bipolar-related networks such as the fronto-temporal and amygdala. This would allow to test as to whether the BD continuum involves atypical brain organisation not only at functional but also at a structural level. If there is a BD continuum, variability in brain organisation should predict transitions from risk BD individuals to BD euthymia and further towards full-blown BD.

Further studies may also look at the relationship between psychosis and BD continuum in terms of FCAs. The investigation of an extended continuum should include euthymic and symptomatic non-psychotic and psychotic BD patients as well as schizophrenic patients. In addition to FCAs such study could implement tasks tapping on response inhibition and dysfunctional emotion regulation (i.e., expression suppression) which have been found to affect both conditions (Gross, 1998, 2002; Gross & John, 2003; Gross & Levenson, 1997). The idea of an expanded BD continuum would not only predict similarities between BD and schizophrenia but also gradually increasing differences between risk BD individuals, BD euthymia, and full-blown BD in terms of these measures. A wide range of emotional and non emotional tasks would allow disentangling more subtle differences between psychosis and schizophrenia. Given that there have been suggestions of an overlap between the two forms of psychosis this approach would allow to delineate the BD-psychosis continuum in further detail.

7.4. Final conclusions

The present study sought to investigate FCAs in emotional processing in two major ways. First, FCAs underlying facial emotion perception have been examined under normal functioning indicating a lack of support for asymmetry models. However, perception of a subset of negative emotions related to distress show a right hemisphere advantage, which may have invoked concomitant emotional experience. Secondly, functional brain organisation in emotional processing was further examined by assessing FCAs in BD euthymia and hypomanic related traits, used as an

experimental model for studying emotional processing. At the lower bipolar continuum there is a right hemisphere dysfunction implicated in emotional processing, as suggested by the findings in individuals with high hypomanic related traits. These results indicated that even subtle alterations in emotion regulation, observed in this condition, are associated with atypical functional brain organisation. In a continuum with the low bipolar end, clinically diagnosed euthymic BD patients exhibited atypical FCAs in emotional processing, involving a reduced right hemisphere advantage. Moreover, compatible with previous findings of pronounced deviations in the organisation of personality (e.g., Healy & Williams, 1989; Jones, 2001; Mansell & Scott, 2006; Scott & Pope, 2003) and FCAs (e.g., Bruder et al., 1981; Yozawitz et al., 1979) in symptomatic BD patients, the reduced FCAs patterns in euthymic BD patients suggested a BD continuum lying in euthymia.

In line with previous studies underscoring a right fronto-temporal role in the processing of emotions (e.g., Anderson et al., 2000; Mendez et al., 2006; Perry et al., 2001; Rankin et al., 2003; Rosen et al., 2002; Tranel et al., 2002), Chapters 3 and 5 suggest that this network is compromised in both, clinical and subclinical BD conditions. This right hemisphere involvement in BD, also extends to emotion unrelated functions. This was shown by Chapter 6 demonstrating reduced right hemisphere specialisation in visuospatial attention and by Chapter 4 revealing atypical connectivity in a right amygdale network.

The present thesis shows that assessing FCAs in euthymic BD patients reflect inherent aspects of BD functional brain organisation that are free from symptomatic influence. These findings encourage a BD continuum model relying on euthymia as a bridging state between usual mood and acute mood phases.

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